ENCEPHALO-MYELITIS FOLLOWING VACCINATION.

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Received for publication June 29th, 1926.

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INTRODUCTION.

AT the London Hospital in July, 1912, encephalo-myelitis was found at necropsy in a lad of fifteen years who had recently been vaccinated. The histological changes in the central nervous system differed conspicuously in many features from those found in poliomyelitis of infantile paralysis, but as there was that year a small epidemic of poliomyelitis in the district

(McIntosh and Turnbull, 1913), it was thought that these differences might be attributed to the direct introduction of the virus at the site of vaccination. The experimental work of Marie (1920) and of Levaditi, Harvier and Nicolau (1922) suggested that the association with vaccination might be a closer one, and a look-out was kept for a similar case in order that material might be subjected to experimental investigation. Such a case occurred on Dec. 7, 1922: a girl of nine years came to necropsy with a diagnosis of tuberculous meningitis; no macroscopic lesions were found except recent vaccination scabs, regional adenitis and slight changes in the central nervous system; rapid paraffin sections demonstrated the same peculiarities in the histological changes in the central nervous system as in the first case. Other cases were quickly recognized in the wards; three patients died and necropsies were permitted upon two. We thus obtained necropsies upon four cases. Material from three other cases was sent to one of us for investigation in 1923. For this material and for notes upon the clinical histories and necropsies we are indebted to the kindness of Drs. Ernest Mallam and A. G. Gibson of Oxford, the Ministry of Health and Professors Langmead and Kettle. The Ministry of Health was informed in December, 1922, and reports upon the histological and experimental investigation of the seven cases were sent in January, 1924, to a commission appointed by the Ministry.

SUMMARIES OF CLINICAL HISTORIES AND NECROPSIES.

The following are summaries of the cases:

Case I.—L. W. C—, male, 15 years.

July 5, 1912, extraction of teeth and vaccination on left arm. On *2nd or 3rd day* after vaccination, headache, loss of appetite. In following days gradual increase in illness. On *13th day* taken to doctor, fainted, taken home, gradually became unconscious. Obstinate constipation; no vomit; temperature 104° F. On *14th day* admitted to London Hospital: drowsy, semi-conscious, turning head from side to side in bed; roused, with apparent resentment, if shouted at or pulled about; would not obey commands. Right pupil larger than left; retention of urine with overflow; jaw, back and left arm rigid; ankle clonus on left; Babinski's sign on both sides. Pulse full, 64. Temperature 103·8° F. On *15th day* knee-jerks lost; squint developed. Temperature 102° to 103·9° F. On *16th day* respiration abdominal. Temperature 101·5° F. On *17th day* after vaccination, July 22, death in early morning.

Lumbar puncture, 14th day: fluid ran freely; numerous white cells, three lymphocytes to one polymorphonuclear; no tubercle bacilli; cultures sterile (Dr. P. N. Panton).

Necropsy, July 23, 1912 (*P.M.* 480, 1912).—Broncho-pneumonia. Acute meningo-encephalo-myelitis. Recent vaccination scabs on left upper arm; acute hæmorrhagic inflammation of left axillary glands. Muco-purulent bronchitis, collapse and slight peri-bronchial pneumonic infiltration in lower lobes of both greatly engorged lungs; bilateral fibrinous pleurisy. Grey infiltration of pulp of spleen. Slight parenchymatous degeneration of kidneys and congested liver. Slight atheroma of commencement of aorta. Sessile adenoma in rectum. Large caseo-calcareous gland in mesentery. No vaccination scars. Well-nourished and developed boy. Body 175·3 cm., 43·6 kilo; brain 1148·2 gm.; liver 1290·2 gm.; heart 212·6 gm.; kidneys 368·7 gm.; spleen 212·6 gm.; thymus 24 gm.

Case II.—C. S—, female, 9 years.

Nov. 20, 1922, vaccination on left arm. On *11th day* after, headache; vomiting; loss of appetite; sleep deep; drowsiness. On *12th and 13th day*, unconscious; incontinence of urine once. On *14th day* admitted to London Hospital: unconscious, could not be roused; lay still; abdomen carinated. Constipation. Pupils dilated, slight reaction to light; convergent squint; *tâche cerebrale:* limbs flaccid; Kernig's and Babinski's signs present on both sides; knee-jerks just obtained. Sighing respiration. Pulse 140, of good volume and tension. Temperature 102° to 103° F. On *15th day*, persistent coma; temperature 101·4° to

99·2° F. On *16th day* temperature 97° to 100° F. On *17th day* after vaccination, Dec. 7, death at 4 a.m.

Lumbar puncture, 14th day: fluid under pressure; 68 white cells per c.mm.; small lymphocytes 59 per cent., polymorphonuclears 41 per cent.; no tubercle bacilli (Dr. P. N. Panton).

Necropsy, Dec. 7, 1922 (*P.M.* 535, 1922).—Acute meningo-encephalomyelitis. Recent vaccination scabs on left upper arm. Œdema of subcutis of left upper arm and axilla. Acute hæmorrhagic inflammation with great swelling of left axillary glands; great injection and slight enlargement of left supra-clavicular glands; very slight enlargement of left cervical and angular glands. A few patches of œdematous collapse in lungs; microscopic purulent bronchiolitis and emphysema in lower lobe of left lung; emphysematous bronchiolectatic cavity (3 cm. diam.) beneath pleura of posterior border of lower lobe of left lung. Early central necroses in Malpighian bodies and slight inflammatory infiltration of spleen. Parenchymatous degeneration of myocardium, liver and congested kidneys. Slight atheroma in innominate artery and at orifice of left coronary artery. Three ascarides in duodenum and ileum; two thread-worms in appendix. Considerable injection of mucosa of urinary bladder. No vaccination scars. Well-nourished and developed girl. Body 121·12 cm., 20·07 kilo; brain 1332·5 gm.; liver 609·6 gm.; heart 99·3 gm.; kidneys 99·3 gm.; spleen 42·5 gm.; thymus 14 gm.

Case III.—F. K—, female, 22 years.

Vaccinated when baby. Nov. 29, 1922, re-vaccinated on left arm. On *7th to 10th day* after vaccination, headache; constipation; abdominal pain; anorexia; thirst; vomiting. On *10th to 12th day*: drowsy, unintelligible; high fever. On *11th and 12th day*, retention of urine; constipation; temperature 104° F. On *13th day* admitted to London Hospital: semicomatose, opens eyes when addressed and mutters unintelligibly; pin-head pustules on face and on left arm near vaccination scab, petechiæ on arms and abdomen; bladder at umbilicus. Pupils small, equal, do not react to light. Limbs flaccid; tendon and abdominal reflexes absent; flexor plantar response; Kernig's sign present. In evening, deepening coma; cyanosis; small vomits. Pulse-rate 120. Temperature 102° to 102·8° F. On *14th day* after vaccination, Dec. 13, temperature 100° F. in morning; died about noon.

Lumbar puncture, 13th day: pressure slightly increased. Fluid blood-stained; excess of protein; many red corpuscles; no apparent excess of white cells (Dr. P. N. Panton).

Necropsy, Dec. 14, 1922 (*P.M.* 554, 1922).—Broncho-pneumonia. Acute meningo-encephalomyelitis. Recent vaccination scabs on left upper arm, with dried pustules in neighbourhood; necrosis and infiltration of adipose tissue beneath scab. Great œdema of subcutis of left upper arm and tissues of left axilla. Congestion, inflammation and great enlargement of left axillary glands. Purulent bronchitis, collapse and nodules of pneumonic consolidation in lower lobe of right lung; slight purulent bronchitis in lower lobe of left lung and scattered throughout remainder of lungs. Slightly enlarged, semi-diffluent, inflamed spleen and splenunculus. Absence of right kidney, ureter, and ureteric orifice in bladder; severe parenchymatous degeneration of hypertrophied left kidney. Unicornuate uterus; absence of right cornu. Congestion, parenchymatous degeneration and focal necroses in liver. Post-mortem digestion, with perforation, of lower end of œsophagus. Mucous catarrh and streaks of altered blood in injected stomach; myoma (0·7 by 0·5 cm.) in submucosa of posterior wall of stomach. Slight general atheroma. Numerous, faint, pink petechiæ on right arm. No vaccination scars. Considerable amount of glandular tissue in thymus. Well-nourished and developed woman. Body 165·1 cm., 46·27 kilo.; brain 1396·3 gm.; liver 1219·1 gm.; heart 241·0 gm.; left kidney 184·3 gm.; spleen 141·75 gm.; thymus 13 gm.

Case IV.—D. S—, female, 12 years.

Nov. 22, 1922, vaccinated on left arm. On *7th day* after vaccination felt ill, listless, stayed from school; arm ached. On *10th day* moderate epistaxis. On *11th day* headache in morning, severe epistaxis and vomiting in evening, incontinence of urine at night. On *12th day* semi-conscious; incontinence of urine and fæces. On *17th day* urine thick with blood. On *18th day* mentally clear; retention of urine; catheterization. On *27th day* admitted to London Hospital: drowsy, conscious but not always intelligible; face drawn and haggard, very pallid. Superficial and deep tenderness in lower abdomen. Limbs conspicuously weak. Arm reflexes very slight; knee-jerks faint; abdominal reflex on right side only; Babinski's sign absent. Incontinence of urine and fæces; blood and pus in urine. Pulse-rate 90; temperature 97·2° to 97·5° F. 28th to 29th day, temperature subnormal. On *29th day*, Dec. 22, sudden collapse and death.

Necropsy, Dec. 27, 1922 (*P.M.* 572, 1922).—Anæmia. Septicæmia. Hæmorrhagic cystitis. Healing meningo-encephalomyelitis. Recent vaccination of left upper arm. Moderate enlargement of left axillary glands. Blood and clot (8 oz.) in urinary bladder; hæmorrhagic ulceration of fundus of dilated and hypertrophied bladder; focal fibrinous peritonitis between fundus and sigmoid colon. Acute hæmatogenous nephritis; petechiæ in left renal pelvis; medullary fibroma in left kidney. Acute inflammation of spleen. Leucocytic infiltration of portal systems of œdematous, congested liver. Mucous catarrh of stomach. Pink fatty marrow in neck and upper third of shaft of femur; pale pink marrow in ribs and sternum. Very slight atheroma of common carotids and aorta. Calcareous gland in ileo-colic angle of mesentery. Very little parenchymatous tissue in thymus. No vaccination scars. Extremely pallid, well-developed girl. Body 35·64 kilo, 146·5 cm.; brain 1311·2 gm.; liver 1034·8 gm.; heart 190·4 gm.; kidneys 269·7 gm.; spleen 113·4 gm.; thymus 6 gm.

Case V.—M. H—, female, 15 years.

Sept. 25, 1923, vaccinated. On *11th day* after vaccination complained of pain in arm and of feeling unwell; headache, anorexia, sickness but no vomit. Dozed in afternoon and evening; fell asleep at 10 p.m. and could not be roused. Bowels not opened for two days; no urine for one day. Twitching of fingers and face observed. On *12th day* admitted to Radcliffe Infirmary, Oxford: unconscious, occasionally moved and groaned; reacted to painful stimuli but did not answer when addressed. Eyes closed; pupils very small, equal, reacted to light. Flaccid paralysis of right leg; both knee-jerks absent; left leg alone drawn up if either left or right foot pinched; doubtful Babinski's sign on left; Kernig's sign positive. Incontinence. Temperature 105°–106° F.; pulse-rate 96; respirations 32. On *13th day*, flaccid paralysis of both legs. On *14th day*, pupils unequal; marked *tâche cerebrale*; petechiæ at bend of left elbow, macules on dorsum of right hand and lower right forearm. Temperature normal. On *15th day* after vaccination, Oct. 10, about 2.20 p.m., œdema of lungs, deep cyanosis, froth from nose; pulse-rate 180; death later.

Lumbar puncture, 13th day: pressure slightly increased; fluid clear.

Necropsy, Oct. 11, 1923.—Broncho-pneumonia. Acute meningo-encephalomyelitis. Recent vaccination on left arm. Purulent bronchiolitis, extensive peribronchial consolidation and more extensive serous, partly hæmorrhagic, exudation in lungs. Parenchymatous degeneration of liver; slight parenchymatous degeneration of kidneys. Soft, enlarged (× 1½), engorged and infiltrated spleen. Well-nourished and developed girl.

Case VI.—K. B—, female, 7 years.

Sept. 29, 1923, vaccinated. On *12th day* after vaccination felt ill and cried; headache; epistaxis. Became drowsy and could not be roused. Temperature 102·8° to 104° to 103° F. On *17th day* after vaccination, Oct. 16, 1923, died.

Necropsy, Oct. 18, 1923.—Broncho-pneumonia. Acute meningo-encephalomyelitis. Recent vaccination on left arm. Enlargement of left axillary glands. Purulent bronchitis, slight peribronchial pneumonia, serous exudate and collapse in lungs, especially bases. Slightly enlarged, soft, grey, infiltrated spleen. Post-mortem degeneration of kidneys; a few hyaline casts in tubules. No vaccination scars.

Case VII.—S. McE—, male, 21 years.

Oct. 3, 1923, vaccinated on left arm. On *2nd day* after vaccination drowsy, complained of pain in abdomen and back, and vomited after food. Similar symptoms to 4th day. On *4th day* admitted to St. Mary's Hospital: drowsy, difficult to rouse and lapsing readily into complete unconsciousness, but able to answer questions. Occipital headache. All four limbs moved; apparently no paralysis. Slight rigidity of neck muscles; nystagmus to right in both eyes; abdominal, plantar and knee reflexes absent; retention of urine with distension; bowels said to have been well opened before admission; marked *tâche cerebrale*. Pulse slow. Temperature normal. On *16th day* unconscious, could not be roused. Slight dilatation of pupils; slight rigidity of arms and legs; retention of urine still. Temperature had been gradually rising. On *17th day* comatose; breathing shallow and rapid. On *18th day* after vaccination, Oct. 21, at 3 a.m., temperature 104° F. and death.

Lumbar puncture, 4th day: no increase of cells; no organisms; culture negative. Blood-count on 17th day: white cells 11,200; polymorphonuclears 62 per cent.

Necropsy, Oct. 22, 1923.—Broncho-pneumonia. Acute meningo-encephalomyelitis. Recent vaccination on left arm. Chronic partially disseminated submiliary tuberculosis. Purulent bronchiolitis; slight peribronchial pneumonic consolidation and more extensive serous exudation in lower lobes of lungs. Fibrotic, granulomatous, submiliary tubercles widely disseminated throughout lungs, liver and spleen. Calcareous mesenteric glands; enlarged fibrotic hepatic and paratracheal glands. Congestion and slight inflammatory infiltration of spleen. Slight post-mortem degeneration of kidneys. Milk spot on left ventricle. Petechial hæmorrhages in pericardium and in digested mucosa of stomach. Post-mortem digestion of œsophagus. Slight atheroma. Large thymus. Spare, well-developed man.

PATHOLOGICAL CHANGES.

(1) *Cause of Death.*

The seven cases fall into two groups. In all the cases except Case IV the subjects died during an acute attack of encephalo-myelitis complicated by broncho-pneumonia. In Case II purulent bronchiolitis was only detected upon microscopic examination of the base of the lungs; in the other cases the broncho-pneumonia was conspicuous to the naked eye.

In Case IV the encephalo-myelitis was in a stage of healing, and death was due to anæmia and septicæmia following severe hæmorrhagic inflammation of the paralysed urinary bladder. The diagnosis of septicæmia was made from the microscopic findings in the kidney, liver and spleen. Gross anæmia was observed at necropsy: in microscopic sections there are a few myeloblasts and neutrophil myelocytes in the spleen and in the vessels of the liver and kidney, but only one or two erythroblasts were identified and there are no areas of myeloid transformation.

(2) *The Central Nervous System.*

A. Acute stage: Cases I to VII, excepting IV.

The abnormalities detected with the naked eye were for the most part slight. In Case I a small patch of red gelatinous clot was lightly adherent to the dura in the right posterior fossa, and a similar patch lay upon the surface of the arachnoid membrane over the postero-mesial angle of the right lobe of the cerebellum. There was also a slight, diffuse hæmorrhage into the leptomeninges over both parietal lobes. There was congestion of the leptomeninges and of the substance of the brain and brain-stem in all cases; the cerebral convolutions were not flattened. In the spinal cords red dots and streaks in portions of the grey matter of particular segments indicated injected vessels, or possibly perivascular hæmorrhages; definite punctiform hæmorrhages were rarely present, for instance in the left anterior horn of the eighth cervical segment in Case II; occasionally all the grey matter on one side of a segment showed a pink flush. Red streaks were rarely present in the white matter. The demarcation between the grey and white matter was blurred in the thoracic and lumbar segments of Cases II and III, and to a less extent in the cervical segments of Case III. In Case V the cord was extremely soft and the grey and white matter could only just be differentiated.

Microscopic examination.—In Case I the microscopic examination of the central nervous system was confined to the right parietal cortex, and the fourth and fifth cervical, the sixth thoracic, and the first and fourth lumbar segments of the spinal cord.

In Case II portions were taken for microscopic examination from the right and left orbital lobes including the olfactory lobes, from the prefrontal and central areas of both hemispheres, both occipital lobes, and the right cornu Ammonis; complete segments were taken from the right and left basal ganglia, the anterior and posterior corpora quadrigemina, the pons at the emergence of the fifth and eighth cranial nerve-roots, the medulla oblongata through the olives, the second, fourth, fifth, sixth and eighth cervical segments of the spinal cord, the third, fifth, sixth and ninth thoracic segments, the first, second, third and fifth lumbar segments, and the second and fourth sacral segments. The following spinal root ganglia were cut longitudinally: the fourth to eighth left and the fourth to sixth right cervical; the first and second sacral left and right.

In Case III the portions removed from the brain and brain-stem were similar, except that the cornu Ammonis was omitted. From the spinal cord were taken the second and fifth cervical, the second, fifth, eighth and twelfth thoracic, the second and fourth lumbar, and the first and third sacral segments. The spinal root ganglia taken were: the fifth to eighth left and right cervical, the first left thoracic, the third and eighth left and right thoracic, three lumbar and two sacral.

In Cases II and III the left side of complete transverse segments was perforated with a hair for identification of lateral distribution.

In Case V the portions examined microscopically were: frontal and parietal cortex, portion of caudate nucleus and putamen, the pons, one cervical, three thoracic and two lumbar segments of spinal cord.

In Case VI: frontal cortex, portion of basal ganglia, pons, upper extremity of cervical cord, two other cervical, two thoracic and one lumbar segment of spinal cord.

In Case VII: portion of basal ganglia, mid-brain, pons and segment of thoracic cord.

Active inflammation is present in all the portions taken except the upper extremity of the cervical cord in Case VI. The inflammation affects the leptomeninges, the white matter and the grey matter. The inflammation of the leptomeninges is relatively slight and insignificant. It consists of a slight infiltration of the pia arachnoid of the brain and of the pia of the cord, and is found chiefly round veins. The meningeal vessels are engorged and frequently contain thrombi, in which leucocytes are usually abundant. There are occasionally hæmorrhages into the cerebral meninges; such hæmorrhage is greatest in Case I.

Within the substance of the brain and cord infiltration is conspicuous and is essentially perivascular. Infiltrations within the adventitial sheaths or immediately round the sheaths of the vessels, forming sharply-defined vascular sleeves, are numerous; but such sleeves are usually narrow, often consisting of no more than a single row of cells. The predominating lesion is a broad zone of less dense, "extra-adventitial," perivascular infiltration (Fig. 1). In portions of the grey matter in which this infiltration is at its maximum the perivascular distribution is less distinct, the infiltration becoming diffuse (Fig. 3). Such zones of extra-adventitial perivascular infiltration occur in the white matter (Fig. 2), but the most characteristic feature of the inflammation is the occurrence in the white matter of a broad perivascular zone of softening in which infiltration is relatively slight (Figs. 4, 6, 7). This softening was demonstrated by the Weigert-Pal method in only one portion of tissue from Case V, but the loss of medullated sheaths is conspicuous in sections stained deeply with hæmatoxylin, particularly Weigert's iron-hæmatoxylin. The loss of the rings corresponding to the medullary sheaths is usually associated with a spongy vacuolation of the glial net; the cytoplasm of the infiltrating cells tends to be vacuolated and occasionally is typically foam-like. The vessels in the centres of these zones usually have no sleeve of adventitial infiltration. The vessels in the substance of the brain and cord are engorged, and hyaline thrombi and fibrinous thrombi containing numerous leucocytes are occasionally present. Hæmorrhages are a comparatively rare feature, and are small and perivascular. There is much tigrolysis, often perinuclear only, of the bodies of neurons. Eccentricity of nucleoli or of nuclei is occasionally seen, but loss of angularity and complete necrosis are very rare. Indeed, the normal appearance of nerve-cells in areas of great infiltration is a striking feature. Definite neuronophagia is not seen, although proliferated glial cells or one or two leucocytes may lie against a nerve-cell.

In *cytology* the infiltrations resemble in general those of the non-purulent inflammations of the central nervous system. The infiltrations of the leptomeninges contain small lymphocytes (*sl.*, Fig. 9), large lymphocytes, of which the larger examples are chiefly of plasmacytoid form, plasma-cells, hyaline cells, and cells with the fibrocytic type of nucleus. The large lymphocytes (*ll.*, Fig. 9) have a spongy cytoplasm as deeply basophil as that of a plasma-cell, and a round or slightly oval nucleus in which the membrane is stout and deeply stained whilst several large oval nodes lie in a scanty net of chromatin; one, seldom more, of the nodes can be resolved into a nucleolus surrounded by chromatin. The plasmacytoid examples (*pd.*, Fig. 9) are of pear or oblong shape and the nucleus is eccentric; a less deeply stained demi-lune is sometimes seen in the cytoplasm, embracing the nucleus on the side of the main mass of the cell-body. The true plasma-cells differ only in that the nucleus contains a central nucleolus whilst the other nodes lie upon the inner side of the nuclear membrane: the "clock-face" nucleus. The plasmacytoid cells measure from 6 to 8 micra in average diameter with nuclei of 4 to slightly over 5 micra. Two nuclei are occasionally present as in the typical plasma-cells. Such plasmacytoid cells, it may be mentioned, are numerous among adventitial cells in various inflammations elsewhere for instance in inflammations of the dermis. The hyaline cells (*h.*, Fig. 9) resemble in the structure and multiform shapes of their nuclei, in their single nucleolus, and the slight basophilia of their cytoplasm the large mononuclear leucocytes or endothelial leucocytes (*hm.*, Fig. 9) of the blood; the nuclei usually show two or three overlapping lobes. The cells with nuclei of the fibrocytic type (*f.*, Fig. 9), that is nuclei with a close mesh of delicate fibrils of chromatin and one or two relatively small nucleoli, are doubtless derived from the cells which lie upon the fibrillar sheets of the leptomeninges and are probably endothelial. The plasmacytoid cells are relatively numerous; in Cases I and II typical plasma-cells containing one or two nuclei of clock-face structure and central nucleolus were easily found, but in Case III only after prolonged search.

In the vascular sleeves similar cells are seen, but here the genesis of the cells with nuclei of the fibrocytic type (*f.*, Fig. 9) is less certain; some lie within the collagenous meshes of the adventitial sheath; others lie upon the outer surface of the adventitia. They are doubtless either fibrocytes or endothelial cells. The large lymphocytes frequently show karyokinetic figures. Neutrophil leucocytes and, very rarely, eosinophil leucocytes also occur. When the infiltration within or immediately outside the adventitial sheath is slight plasmacytoid cells usually predominate, or are alone found. When the infiltration is greater hyaline cells and cells with nuclei of the fibrocytic type may be conspicuous. In the larger sleeves all the types of cell are present, small lymphocytes and neutrophil leucocytes generally being relatively numerous whilst the plasmacytoid cells are relatively scanty. Neutrophil leucocytes are occasionally amongst the earliest cells. The hyaline cells very rarely contain remnants of ingested cells. In general it may be said that small lymphocytes are not so numerous as to obscure the other cells, plasmacytoid cells are conspicuous in sections stained with the Unna-Pappenheim mixture, and neutrophil leucocytes (Fig. 10) are present in considerable number in the intenser areas of inflammation; typical plasma-cells are scanty.

In the extra-adventitial, perivascular or diffuse, infiltrations most of the cells are free glial cells and neutrophil leucocytes, whilst lymphocytes and plasmacytoid cells are rare. The glial cells are sometimes of stellate shape with homogeneous cytoplasm, but they are usually rounded whilst their nuclei are elongated and twisted and their cytoplasm is vacuolated. The leucocytes also tend to have a vacuolated cytoplasm, losing their specific granules. In the areas of greatest infiltration neutrophil leucocytes are fairly numerous (Fig. 10), but most of the cells are glial.

The distribution of the inflammatory infiltration.—Infiltration of the meninges is everywhere slight, and is intermittent and focal in distribution. It tends to be greatest round veins. Infiltration of the anterior septum of the spinal cord is usually very slight: it is abundant in some segments where there is great infiltration of the spinal substance, but is only abundant in the dorsal portion of the septum; on the other hand it may be very slight or absent when there is very great infiltration of the spinal substance (Fig. 5).

Infiltration of the substance of the brain and cord is present in all sections examined except the first segment of the cervical cord in Case VI.

In all the 20 segments of the cerebral hemispheres a varying number of vessels in the medulla show narrow sleeves of infiltration, usually composed of a single row of cells; round many of these vessels is a zone of cellular infiltration (Fig. 2), round others in 10 segments is a zone of softening. In no less than 18 segments vessels in the cortex show sleeves and in 17 segments zones of extra-adventitial infiltration (Fig. 1). Vascular sleeves are seen in all layers of the cortex; zones of perivascular infiltration usually lie in the deeper third or half of the cortex, and never extend above the layer of small pyramidal cells. In many sections the involvement of the cortex is greater than of the medulla. In the section of the hippocampus only one vessel shows a sleeve and a zone of infiltration, whilst there are two such vessels in the alveus and several in the grey and white matter of the adjacent hippocampal and temporo-occipital convolutions.

The basal ganglia are affected in all cases but the affection is relatively slight. Vascular sleeves and extensive zones of perivascular infiltration are numerous in the subthalamic region, the amygdaloid nucleus, the external capsule and claustrum; they are as numerous or slightly less numerous in the optic thalamus, the ventral portion of the nucleus usually being more affected than the dorsal. The pulvinar (Case II) is somewhat more severely affected. The affection of the putamen is much less, that of the globi pallidi and of the caudate nucleus, save on the left side in Case II, still less or absent. The cortex and medulla of the insula is somewhat more affected than the optic thalamus.

In the mid-brain the inflammation is greatest in the substantia nigra: there are large patches of perivascular infiltration in the caudal extremity in Case II and in the mesial part of the cephalic portion on both sides in Case III; but there is little or no implication of the remainder of the nuclei, so that taken as a whole they are not severely affected. The internal and external geniculate bodies (Case II) are almost as severely affected. Inflammation of the cephalic part of the oculomotor and trochlear nucleus is very slight, but in the caudal part it is considerable in Case III and severe in Case II: focal tigrolysis and karyolysis are conspicuous in the oculo-motor nucleus beneath the right anterior colliculus in Case II. The tegmentum is slightly more infiltrated. In the peduncles a few vessels have narrow sleeves and in Case III one is surrounded by a zone of softening. The corpora quadrigemina are only slightly affected in some segments.

The affection of the basal portion of the pons is greater than in any other part of the brain and brain-stem in all 5 cases from which sections are available. In Case VII the section consists only of a small part of the most basal portion of the pons, and in this the white matter is more affected than the pontine nuclei. In the other 4 cases the incidence is upon the pontine nuclei: almost all the nuclei are affected, the vessels being surrounded by an infiltration which is so extensive as to become diffuse (Fig. 3), whilst the white matter is softened in the neighbourhood of the larger vessels in the nuclei. The dorsal portion of the pons is almost as severely affected, except the grey matter of the floor of the fourth ventricle; there are some perivascular zones of softening in the fillet in Case II. There is a slight affection of the principal and accessory motor nuclei of the trigeminus in Case II, but these nuclei and the upper sensory nucleus are free in Case I.

At the upper extremity of the medulla the olives are severely affected, showing extensive zones of perivascular infiltration. The peduncles are severely affected in Case III and contain zones of perivascular softening. There is considerable inflammation of the left ventral or accessory cochlear nucleus (Case III), the substantia reticularis and the chief vestibular nuclei. In the centre of the medulla (Case III) the olives are severely affected, whilst the hypoglossal, dorsal vago-accessory, descending vago-glossopharyngeal nuclei, the nucleus ambiguus and the median raphe are almost as greatly infiltrated; there are zones of perivascular softening in the median raphe and the left peduncle. In Case II, however, the section from the lower extremity of the medulla only shows sleeves and perivascular infiltration in the right substantia gelatinosa.

In all 45 segments of the spinal cord, except the upper part of the first cervical in Case VI, there is some infiltration of the white or grey matter or of both. The infiltration is, in general, slight in the upper cervical region but becomes considerable or great about the fifth segment; it then continues of about the same amount or increases until the lumbar region; here it reaches its maximum (Fig. 5), to decrease again in the lower sacral segments. In Case II the left side, the side of vaccination, from the fifth cervical segment to the sixth thoracic is much more infiltrated than the right, and there are hæmorrhages in the sixth cervical segment; in Case III, however, in which only two cervical segments were examined, the right side of the second segment is more infiltrated than the left and the right side of the fifth segment is almost as severely affected as the left, though there is hæmorrhage and much tigrolysis on the left side. In the segments most severely affected, particularly the lumbar, the perivascular sleeves are larger than in the remainder of the cord and brain. The most striking feature is the broad zones of softening, with relatively little infiltration, in the white matter (Figs. 4, 6 and 7). These are found in all white columns but are most frequent in the lateral and antero-lateral. In the first sacral segment in Case III, a lumbar segment in Case V and the thoracic segment in Case VII there is a zone of softening and infiltration along each edge of the anterior septum although the infiltration of the septum itself is very slight (Fig. 5); in the lumbar segment of Case VI a similar zone is associated with considerable infiltration of the anterior septum. In the ventral and dorsal horns are areas of perivascular infiltration; these may occupy any position, but affect especially the lateral portions of the ventral horns where vessels with zones of perivascular softening impinge upon the grey matter (Fig. 6). In the more severely affected segments the perivascular infiltration in the ventral or dorsal horns becomes confluent and the grey matter is more or less diffusely infiltrated (Fig. 5).

The anterior and posterior roots, the 30 posterior root ganglia and the nerves attached to the ganglia are not infiltrated.

The incidence upon special portions of the different levels of the central nervous system from the convexities to the lower sacral segments has been described; a comparison of the general incidence upon these levels shows that the inflammation is maximal in the lumbo-sacral cord and in the pons, and is fairly evenly distributed throughout the whole of the remainder, being at its least or nearly at its least in the upper cervical cord. The grey matter is more affected than the white. But the affection of the white matter is great, particularly in the spinal cord: in the few sections of the spinal cord in Case I the affection of the white matter actually preponderates.

The chief *characteristics of the inflammation* are: the number and size of zones of extra-adventitial perivascular infiltration in comparison to the development and size of adventitial vascular sleeves; the obvious perivascular distribution of the infiltrations; the conspicuous zones of softening with relatively little cellular infiltration that surround vessels in the white matter; the large extent to which the white matter is involved, although the involvement of grey matter is actually greater; the extensive involvement of both cerebral cortex and spinal cord; the incidence of the maximal inflammation upon the lumbar and upper sacral cord, and the pons; the close similarity in the type and incidence of the inflammation in all cases. The most characteristic histological feature is the zone of perivascular softening in the white matter.

B. Subacute Stage: Case IV.

In this case the examination of the central nervous system with the naked eye was complicated by the necropsy having been delayed until the fifth day after death; the brain and cord were very soft. The cerebral convolutions were not flattened; the meninges and brain were anæmic. In the spinal cord there were a few red dots and streaks in various segments; the demarcation between the grey and white matter was blurred; the left anterior horn in the seventh cervical segment was cracked; both anterior horns were pultaceous in the eighth cervical segment; both were sunken and narrow in the first thoracic segment; the left anterior horn was relatively narrow in the third thoracic segment.

Portions were taken for microscopic examination from the right and left prefrontal, central and occipital regions of the hemispheres; complete segments were taken from the right and left basal ganglia, the anterior and posterior corpora quadrigemina, the pons at the level of the roots of the fifth cranial nerve, the medulla oblongata at the emergence of the eighth cranial nerves and through the centre of the olives, the first, fourth, sixth and eighth cervical segments of the cord, the second, fifth and ninth thoracic, the first, second, third and fifth lumbar and the first and third sacral. A hair was passed through the left side of complete segments.

Evidence of inflammation is present in all these regions. Infiltration of the leptomeninges is only present in a few places and is slight. Small perivascular hæmorrhages are only seen in the left occipital lobe and in the second and fifth thoracic segments. Perivascular sleeves are very rare in the hemispheres, being found only in the right occipital lobe, but are fairly numerous in the basal ganglia, whilst one or two occur in all segments of the mid and hind brain, and in the fourth cervical, eighth cervical, third lumbar, fifth lumbar and first sacral segments of the spinal cord. These sleeves are formed by an infiltration which is usually confined almost entirely within adventitial sheaths. The infiltrating cells include all those found in the acute cases; but with few exceptions they are large and small lymphocytes, plasmacytoid cells and cells with fibrocytic nuclei, the latter anastomozing to form a net or lying close upon a net of collagenous fibrils; a few typical plasma-cells are present. The zones of more diffuse perivascular infiltration in white and grey matter, and the zones of perivascular softening of the white matter that were seen in the acute cases, are replaced by zones in which spaces between the glial fibrils contain swollen fat-granule cells, or, much more often, by zones of early gliosis (Fig. 8), in which the glial fibrils are close together and spindle nuclei are numerous and are often arranged in an approximately radial manner round the vessels; free round-cells are rare in these zones of early gliosis, and are for the most part fat-granule cells. The zones of gliosis are found here and there in the white matter throughout, but are most conspicuous in the medulla of the cerebral hemispheres and in the spinal cord; all white columns in the cord are affected. In the medulla of the cerebral hemispheres, and in the white matter of the spinal cord (Fig. 8), the sheath of the vessel in the centre of such an area of gliosis is sometimes filled completely with swollen foam-cells: under low magnifications the wall of such a vessel appears as a broad pale ring.

In the grey matter are similar areas of gliosis; these are usually distinctly perivascular, but in the third sacral segment the gliosis is diffuse. Gliosis in the grey matter is shown by an abundance of spindle nuclei; it is sometimes associated with an obvious loss of the bodies of neurons. The cerebral cortex is intact, except occasionally when at its junction with the medulla it is involved by the periphery of an underlying area of perivascular gliosis. There are a few areas of gliosis in the substantia nigra, but it is difficult to be certain of a loss of neurons because in the normal nucleus the grouping of the cells is irregular. In the pontine nuclei there are several narrow zones of gliosis round vessels, and any loss of ganglion cells appears to be confined to these areas. In the olives one or two small areas of gliosis appear to be associated with a loss of cells. In the spinal cord areas of gliosis are numerous in all segments except the first cervical, and the loss of ganglion cells is undoubted. There is an obvious diminution of groups of cells either in the anterior or the posterior horns or in the columns of Clarke; the anterior horns on one or both sides are affected to a greater or less degree in all segments save the first cervical, and the ventro-mesial column of cells is especially affected. The loss of cells in the anterior horns appears to be as great in the cervical as in the lumbar cord. The grey matter is extremely vacuolated and cracked in the sixth cervical to fifth thoracic segments, but this is probably the result of post-mortem softening: the necropsy was performed on the fifth day after death. The general softening of the cord found at necropsy in this region makes it impossible to decide whether a great reduction in the size of the right horn in the eighth cervical segment is not due to manipulation. A great dilatation of the perineuronic spaces in the oculomotor nuclei, associated with a remarkable distortion of the cells, and a similar but less pronounced change in the substantia nigra are also probably artefacts.

The lesions in this fourth case are such as would be expected in the healing of those seen in the six acute cases. They have the same general distribution; but they are smaller and fewer, the foci of intenser acute inflammation having commenced to scar whilst the less intense, more diffuse infiltrations have apparently undergone complete resolution.

(3) *The Path of Infection.*

Sections of the proximal and distal ends of the right and left brachial plexuses were taken in Cases II, III and IV, in order to determine whether there was evidence of a spread of infection along nerves from the arm to the central nervous system. The proximal end corresponded to a section close to the junction of the nerves to form trunks, whilst the distal end was a section through the cords or through the branches immediately beyond the cords.

The vessels in the plexuses in Cases II and III are engorged, and there are extravasations of blood in the distal ends of the left plexus of Case II and of the right and left plexuses of Case III. In the distal end of the left plexus in Case III there is an infiltration with round-cells about vessels in the common fibrous sheath of the cords and in the adipose tissue. The infiltration lies both within and external to the vascular adventitia. The cells are small lymphocytes, large lymphocytes, free cells of the fibrocytic type, and a few plasma-cells, hyaline cells and neutrophil leucocytes. There is no infiltration within nerve-bundles.

The hæmorrhages are probably extravasations of blood from the engorged vessels into the tissues after death during the dissection for the removal of the plexuses; undoubted inflammation is only present in the distal extremity of the left plexus in Case III. In Section (2) it has been noted that there is no infiltration of the roots entering or leaving the cord, nor of the posterior root ganglia and the nerves immediately distal to the ganglia (Cases II and III); further, although the spinal cord in the cervical and upper thoracic segments is much more affected on the side of vaccination in Case II, a similar homolateral distribution is not found in Case III. There is, therefore, no direct evidence in the sections of an extension along nerves of the inflammation from the vaccinated areas to the spinal cord. There is only evidence that in Case III the inflammatory reaction about the site of vaccination extended as far as the distal end of the left brachial plexus.

(4) *The Vaccinated Areas.*

As a control to the histological examination of the vaccinated areas and regional glands material was taken from a boy, aged eight years, who was brought dead into the London Hospital on December 11th, 1922 (P.M. 551, 1922). His heart and other viscera had been ruptured in an accident. There were recent vaccination scabs on the left upper arm, the arm in their neighbourhood being still œdematous, but the actual date of vaccination was not obtained.

In segments of the left hippocampus, mid-brain, medulla oblongata and the spinal cord at various levels in this control case there were no histological abnormalities except small hæmorrhages in the grey matter of the fifth cervical segment of the cord. The Nissl bodies in this segment and elsewhere were in perfect condition and there was no trace of infiltration anywhere, so that these small hæmorrhages cannot be accepted as evidence of inflammation of the central nervous system.

The vaccinated areas were in all cases upon the outer surface of the left upper arm, and in no case were there scars of a previous vaccination.

There were three areas in Case III, and four in the control and other three cases; their average diameters were in Case III larger and in Case IV smaller than in the control. All were covered by hard dry crusts of dark toffee colour, but in Case III one crust was surrounded by a hard flat zone (0·2 cm. wide) resembling apple-jelly, and another by a zone of hard nodules (0·3 cm. diam.) of similar appearance, whilst a dozen similar, sharply defined nodules lay between the three areas. In no case was any pus visible on lifting the crusts. On section the areas in the control and in Cases II and IV appeared as hard flat sharply defined zones of dark brown or brownish red, measuring respectively in depth 0·1, 0·15 and 0·1 cm. But in Cases II and III a similar brown zone, 0·1 to 0·3 cm. deep, was succeeded by a zone of flat opaque yellowish tissue, 1·5 (II) and 1·2 cm. (III) deep. The subcutis beneath and about the areas was œdematous in all cases except IV, and was so œdematous in Case III that water exuded spontaneously.

Microscopic examination.—In the control case the greater part of the crust consists of greatly swollen, necrosed Malpighian epidermis, infiltrated with serum and traversed by clefts filled with necrosed cells, of which the majority can be identified as neutrophil leucocytes. Above this lies a layer of less altered, but degenerated and necrosed, Malpighian epidermis, including the stratum granulosum; the stratum corneum is usually separated therefrom by coagulated serum infiltrated with neutrophil leucocytes. The deepest part of the crust includes a zone of necrosed dermis.

Beneath this crust is a narrow zone of dermis which is infiltrated with red corpuscles and very numerous degenerated and necrosed leucocytes.

Beneath this a dense infiltration, obviously perivascular in distribution, extends throughout the dermis on either side of the crust, and is present throughout the subcutis in the form of narrow zones round the vessels and lymphatics. The infiltrating cells are small lymphocytes, large lymphocytes with deeply basophil cytoplasm and conspicuous nuclear nodes, hyaline cells, round, polygonal and spindle fibrocytes, eosinophil and neutrophil leucocytes, and plasma-cells. Of these the lymphocytes and plasma-cells are the most numerous, but the number of eosinophil leucocytes is considerable.

In Case II a greater depth of dermis is necrosed and included within the crust, the zone of purulent infiltration immediately beneath the crust is deeper and less hæmorrhagic, and the subjacent infiltration of the dermis and subcutis is slightly greater. Eosinophil leucocytes and round and polygonal fibrocytes are more numerous.

In Cases I and III the infiltration forming the lowest layer is greater and involves more of the dermis and subcutis. Further it is for the most part necrosed. Where it is not necrosed it resembles that in the control except that eosinophil leucocytes are more abundant and plasma-cells are less numerous. Where it is necrosed it is permeated by a net of fibrin, and contains numerous red corpuscles and degenerated and necrosed neutrophil leucocytes in addition to ghosts of the cells seen where the infiltration is not necrosed.

In Case IV the crust is small, there is less dermal infiltration than in the control and there is extremely little infiltration of the subcutaneous fat. Lymphocytes predominate in the infiltration. A new feature is the presence of numerous fat-granule cells where loculi of adipose tissue within the dermis are involved in the infiltration.

Bacteria.—In the control case the only bacteria detected were two or three Gram-negative bacilli and one Gram-positive bacillus in the coagulated serum on the surface of the crust. In Case I the crust contains numerous Gram-positive cocci, diplococci and staphylococci, and the necrosed infiltration beneath contains a few Gram-positive diplococci and an occasional Gram-positive bacillus. In Cases II and IV there are a few and in Case III many staphylococci in the epidermis of the crust, but no organisms in the infiltration beneath.

The histological changes in the vaccinated areas of the control case and of the cases of encephalo-myelitis appear to be essentially similar. Such variations as are present are of degree rather than of kind, and can be explained by differences in intensity and in time relations of infections by one and the same virus. The inflammatory reactions in Cases I and III are certainly of much greater intensity than in the control. In Case IV the reaction appears to be in process of resolution.

(5) *Regional Lymphatic Glands.*

In the control case and in Cases I, II and III the left axillary glands were conspicuously enlarged in comparison with the right. They were all obviously inflamed, their cut surfaces being bulged and soft owing to infiltration. In Cases II and III œdema of the adipose tissue in the left axilla was noted. In the control case the cut surfaces of the glands were pure white; in Cases I, II and III they were hæmorrhagic: "thickly speckled with deep red points," "a deep mahogany red, flecked with small grey areas," "deep mahogany red."

In Case II the left supraclavicular glands and cervical glands at all levels were also larger than the right. In Case IV the left axillary glands were slightly larger than the right. Their cut surfaces were flat and grey.

Microscopic examination.—In the control case a left axillary gland is not congested. There is perivascular infiltration of the capsule, of the fibrous tissue of the hilum and of the adipose peri-adenoid tissue, with small lymphocytes, large lymphocytes with deeply basophil cytoplasm, and eosinophil leucocytes. A few of the deeply basophil cells have the nuclei of plasma-cells; the eosinophil leucocytes form a conspicuous feature of the infiltration. The so-called "germ centres" are very large. The adenoid strands are crowded with lymphocytes, but scattered throughout there are many larger (7 to 8 μ) mononuclear cells with deeply basophil spongy cytoplasm and two or three large, oval nucleoli. Many of these large basophil mononuclear cells show karyokinesis. There are also a few eosinophil leucocytes. The sinuses are narrow and ill defined; they contain lymphocytes, the large basophil mononuclear cells, a few neutrophil and eosinophil leucocytes and a few free endothelial cells.

The chief difference in the left axillary glands of the cases of encephalomyelitis is the blood content in the acute cases I, II and III. The glands are conspicuously congested in these three cases; red corpuscles distend the sinuses in I and there are many large hæmorrhages within the adenoid strands; in II red corpuscles are less numerous in the sinuses and the hæmorrhages are much fewer and smaller; in III red corpuscles are sparse in the sinuses and there are no hæmorrhages. In the convalescent case IV the vessels are not congested, but the sinuses contain a considerable number of red corpuscles.

Other differences are the absence of "germ centres" in Cases I and III, and their small size in Case IV; the absence of eosinophil leucocytes from the peri-adenoid infiltrations in I, III and IV; a slightly larger number of large basophil mononuclears and eosinophil leucocytes in the adenoid strands in II; the presence in the sinuses of III and IV of many foam-like endothelial cells, of which a few contain red corpuscles; the absence in IV of karyokinetic figures in the large basophil mononuclears.

The right axillary glands in the control case and the four cases of encephalitis differ from the left in the following respects. Congestion and peri-adenoid infiltration are present only in Case III; the infiltration is slight and consists of lymphocytes alone. "Germ centres" are present on this side in the control case alone, and are much smaller than on the left. In the adenoid strands there are fewer large basophil mononuclears; karyokinesis is rare or absent in these cells; eosinophil leucocytes are very sparse or absent.

The regional glands, therefore, of the control and encephalo-myelitic cases are the seat of an inflammation of essentially similar cytology: a non-purulent inflammation in which a greater or less degree of infiltration with eosinophil leucocytes is a feature. Such differences as are present in the inflammatory reactions do not suffice to indicate an essential difference in the infecting agents.

(6) *The Spleen.*

The spleen was inflamed in all seven cases; microscopic examination was made in all save Case I. In Case II the pulp is infiltrated with large lymphocytes and larger basophil cells, many of the latter showing karyokinesis. In

Case VII there is a slight infiltration with these basophil mononuclear cells. In Case III a great increase in basophil mononuclears is associated with an increase in the number of neutrophil leucocytes. Both types of cells are increased in Cases V and VI, the increase in neutrophil leucocytes being great in VI. In the convalescent Case IV there is a great increase in the number of neutrophil leucocytes, but only a slight infiltration with basophil mononuclears.

In Case IV the inflammation of the spleen is obviously part of the terminal septicæmia. In the other cases the acute encephalo-myelitis was complicated by purulent broncho-pneumonia. The degree and type of infiltration of the splenic pulp corresponds very closely with the degree and stage of the broncho-pneumonia in the different cases, so that the inflammation is probably a consequence of this complication and cannot be accepted as due to the excitant of the encephalo-myelitis.

(7) *Other Tissues.*

Microscopic examination was made of the *lungs* in Cases II, V, VI and VII, of the *liver* and *kidney* in Cases IV, VI and VII, and of the *urinary bladder* in Case II. The results have been incorporated in the summaries of necropsies. By an unfortunate accident no microscopic examination was made of the focal necroses in the liver in Case III.

EVIDENCE OF ÆTIOLOGY DERIVED FROM CLINICAL AND HISTOLOGICAL MANIFESTATIONS.

Clinical Histories.

Five of the seven patients were female and two male; their ages varied from seven to twenty-two years. In four cases the illness commenced with headache, malaise and anorexia, accompanied in three by vomiting or a feeling of sickness and also in two by pain in the abdomen or arm; in one case it commenced with headache and epistaxis; in two cases the headache followed two and four days after vomiting with pain in the back and after pain in the arm respectively. Drowsiness was also an initial symptom in four cases, but appeared later in three. This drowsiness increased with varying rapidity to complete or almost complete unconsciousness on the eleventh to thirteenth day, and fever of from 102° to 105° was noted about the same date About this time or before it there was incontinence of urine or retention with distension of the bladder whilst the bowels were obstinately constipated or, in one case, incontinent. The pupils were examined at this time in five cases and were found to be unequal, small, very small and unequal two days later, or dilated (two cases). A squint was also present in two cases; there was no reaction to light in a third; nystagmus had been present twelve days earlier in a fourth. Kernig's sign is mentioned in three cases. Some rigidity of limbs was noted in two, flaccidity in three cases. Babinski's sign was present in two and doubtful in one; the plantar response was flexor in a fourth and absent in a fifth. The knee-jerks in the later stages were just obtained in one and were absent in the other four in which they are mentioned. *Tâche cerebrale* was noted in three.

Death in six cases occurred on the fourteenth, fifteenth, seventeenth (three) and eighteenth days after vaccination. In the other case, IV, consciousness was regained on the eighteenth day but the patient remained drowsy, retention of urine and incontinence of fæces persisted, the abdominal reflexes were absent on the left side, the arm and leg reflexes were feeble, and death from anæmia and septicæmia in consequence of hæmorrhagic inflammation of the bladder occurred on the twenty-ninth day after vaccination. In the fourth fatal case in 1922, in which necropsy was refused, a girl of twelve had severe headache, vomited and became drowsy on the twelfth day after vaccination; on the thirteenth day she was unconscious, irritable and noisy, the arms were rigid, the abdominal, ankle and plantar reflexes were absent and there was distension of the bladder with incontinence of urine and fæces; on the fifteenth day the stupor had deepened, the legs were paralysed and the knee-jerks absent. On the evening of the sixteenth day she regained consciousness and spoke sensibly, but broncho-pneumonia caused death on the nineteenth day. In a case which Dr. Theodore Thompson kindly invited us to see in 1925 a boy of ten was vaccinated on May 30, felt ill and vomited on the fifth day after vaccination, became constipated later, had headache on the eleventh day and vomited and was drowsy on the twelfth. On the thirteenth day ptosis was observed, the legs were rigid and Kernig's sign was present. On the sixteenth day Babinski's sign was present, the knee and ankle-jerks were absent and coma was deeper. On the twentieth day he became less comatose and spoke a few words sensibly. On the twenty-sixth day the plantar response was flexor, and on the thirtieth day after vaccination he had recovered completely. Such complete recovery appears to be the rule in cases that survive, but Dr. Riddoch has kindly told us of a case in which after five years there are still defective sensibility to pain, heat and cold in and below the ninth thoracic segment, and incontinence of urine and fæces in cold weather or when the patient is tired or has taken laxative medicine. This patient, a girl of twenty-one, was vaccinated on May 25, 1921; felt ill, had retention of urine, shivering and a temperature of 102° F. on the twelfth day after vaccination; could not stand or walk on the fourteenth day; had lost sensation completely below the waist on the seventeenth day; began to recover sensibility and voluntary power on the twenty-first day, but had slight spastic paresis of the lower limbs when admitted to hospital on the thirty-fourth day after vaccination. We know of no case in which permanent paralysis of limbs resulted.

Possible Causes.

The resemblance between the clinical histories is almost as great as between the histological findings. The periods after vaccination at which consciousness was lost, at which alterations in the pupils, rigidity and paralysis of limbs and paralysis of the bladder were observed, at which death occurred or consciousness was regained are remarkably similar, except in Case VII in which paralysis of the bladder and loss of reflexes were observed as early as the fourth day after vaccination. Similar cases independent of vaccination were not observed at the same nor any other time. In view of the close resemblance between the clinical histories, the uniformity of the pathological findings and the absence of similar cases independent of vaccination, there can be no doubt that vaccination was a definite causal factor and no chance coincidence: the condition was undoubtedly a post-vaccinial encephalitis.

The encephalitis might have been caused by the vaccinia virus, by some other virus introduced in the vaccinial lymph, by some virus contaminating the wound of vaccination or, as has been suggested in explanation of the cases in Holland (Bastiaanse, etc., 1925), by vaccination provoking a virus latent within the patient. It is unlikely that the lymph was contaminated, because we are informed that the source of the lymph differed in different cases. There is no histological evidence (pp. 193–195) of contamination of the vaccination wounds: the inflammatory reaction in the scabs and in the regional glands appeared to be that of vaccinia of somewhat exceptional intensity. Here it may be mentioned that the histological examination does not give direct evidence of the introduction of the infecting agent at the site of inoculation, because no evidence was found (pp. 192–193) of extension of the inflammation along nerves to the spinal cord. Histologically the encephalo-myelitis belongs to the non-purulent group, and among the known members of the group finds its closest affinity in poliomyelitis (Heine-Medin's disease) and lethargic or epidemic encephalitis (Economo's disease). The general resemblance to these two forms of inflammation is so close that it is obviously necessary to inquire whether the histological or other evidence points to the viruses of either of these two diseases being the actual infecting agent.

Seasonal and Annual Incidence in Relation to other Encephalo-myelitis.

The dates of illness in the 10 cases of which clinical histories have been given above were: 1 case in the last week of May, 1921; 2 cases in July, 1912 and 1925; 3 cases at the end of September and commencement of October, 1923; 4 cases in the last week of November and first of December, 1922. The bulk of the cases, therefore, occurred between the end of September and beginning of December. It is now recognized that poliomyelitis and encephalitis lethargica have definite, independent seasonal variations: the maximal incidence of poliomyelitis is reached in autumn about September, whilst that of encephalitis lethargica is reached in the spring about March. The seasonal incidence, therefore, of the cases of post-vaccinial encephalitis did not correspond to that of either poliomyelitis or encephalitis lethargica.

In 1912, 3 cases of poliomyelitis were found at necropsy in the London Hospital, 1 earlier (April 24) and 2 later (Sept. 28, Oct. 25) in the year than the case of post-vaccinial encephalitis, but in 1921 and 1922 there were no examples of poliomyelitis at necropsy. In 1918 encephalitis lethargica was found in 9 necropsies, in 1919 in 2, in 1920 in 15, in 1921 in 6, but in 1922 in none and in 1923 in 2 only (end of June and September). If the incidence at necropsy is accepted as an indication of the prevalence in the district of the three conditions, then the post-vaccinial encephalitis was prevalent in years when poliomyelitis and encephalitis lethargica were in abeyance.

The number of cases is so small that the significance of the results of the above analyses is doubtful. It can only be said that the data at our disposal demonstrate no association in time between the post-vaccinial encephalitis and poliomyelitis or encephalitis lethargica; and they bring evidence against the assumption that the post-vaccinial cases were merely examples of either poliomyelitis or encephalitis lethargica in which vaccination was an immaterial accident. But they bring no evidence against the possibility of post-vaccinial encephalitis representing a smouldering infection with either of these viruses set alight by vaccination. Clearly in such circumstances the seasonal and annual incidence would depend upon two factors—the prevalence of the infections and the prevalence of vaccination in the district. These two factors we are not in a position to examine. In Holland (Bastiaanse, etc., 1925) 8 cases of post-vaccinial encephalo-myelitis occurred in 1924, of which 5 fell in September. Of 26 cases in 1925, 16 were in March, 7 in April, and 2 in February; of 96 cases of encephalitis lethargica in 1925, 35 fell in March, 20 in April, and 14 in February, whilst there were 12 in January and 10 in May. In Holland, therefore, there was a close parallel between the incidence of post-vaccinial encephalitis and encephalitis lethargica in 1925; and it was chiefly upon this epidemiological evidence that it was considered most probable that the vaccination had provoked a latent encephalitis lethargica. But this correlation cannot be accepted as established in view of the absence of an examination of the relations to the prevalence of vaccination.

Histological Comparison with Poliomyelitis.

The lesions of poliomyelitis resemble those of the post-vaccinial cases more closely in their extent of distribution than in their histological details.

Distribution.—In all fatal cases of poliomyelitis in which we have cut sections above the level of the spinal cord there has with only one exception been considerable inflammation as far at any rate as the basal ganglia. In the exception the only evidence of inflammation above the cervical cord was a slight infiltration of the adventitia of a vessel in the ventral part of the grey matter of the iter at the level of the anterior corpora quadrigemina. In 9 other cases in which the cerebral hemispheres were examined, including 3 from which monkeys were successfully inoculated, adventitial sleeves were found in the medulla in 8 and in the cortex in 6; there were foci of extra-adventitial infiltration in the cortex in 5. As in the post-vaccinial cases this extra-adventitial infiltration lay chiefly in the deeper layers of the cortex but occasionally implicated the layer of small pyramidal cells. In the basal ganglia the optic thalamus, especially its ventral part and the pulvinar, and the subthalamic region were most affected. The mid-brain was only examined in 3 cases; the grey matter of the aqueduct and the substantia nigra were affected in all 3, the corpora quadrigemina in 2. The pons and medulla were infiltrated in all cases, the lower medulla being somewhat less affected than the upper. The cord was severely affected. But there are definite differences in the distribution. The implication of the cerebral hemispheres is much less widespread than in the post-vaccinial cases; the foci of extra-adventitial infiltration are scanty and are only found in sections from the Rolandic area. In only 1 of the 3 cases in which the mid-brain was examined is the infiltration greatest in the substantia nigra. In the pons the infiltration is almost limited to the dorsal portion, there being little or no infiltration of the pontine nuclei. At least one portion of the spinal cord is considerably more severely affected than any other part of the central nervous system. The lumbar cord is more affected than the cervical in only 6 out of 11 cases. Meningeal infiltration is in general greater in poliomyelitis, and is conspicuously greater in the pia in the anterior fissure of the spinal cord. Finally the infiltration in the white matter is almost entirely confined to the adventitia of vessels, the inflammation being essentially an inflammation of grey matter.

Histological details.—All the cells in the infiltrations of the post-vaccinial cases, with the exception of true plasma-cells, are found in poliomyelitis; the largest of the "large lymphocytes" of this paper were in a previous communication (McIntosh and Turnbull, 1913) called "lymphoblasts." But in poliomyelitis large lymphocytes are relatively scanty and plasmacytoid cells are rare; true plasma-cells we have not yet found; we mentioned their occurrence in our previous communication, but the statement depended upon the acceptance of Case I as a peculiar type of poliomyelitis due to infection at the site of inoculation. Neutrophil leucocytes are more abundant in the adventitial and extra-adventitial infiltrations. In poliomyelitis vascular sleeves are in general larger and a much more prominent feature, and the sleeves are usually formed by an infiltration confined within the adventitia. The perivascular nature of the extra-adventitial infiltrations is not conspicuous; the areas of infiltration in the grey matter, very rarely in the white matter, are usually seen as rounded foci densely packed with free cells; these foci originate as a rule round small capillaries, but the central capillary becomes obscured so that they are not obviously perivascular like the less dense zones of infiltration that extend round vessels in the post-vaccinial cases. Areas of conspicuous softening of the grey matter of the spinal cord are almost constant in poliomyelitis, but were not found in the post-vaccinial myelitis. Necrosis of nerve-cells and peri-neuronic infiltration (neuronophagia) are both greater in poliomyelitis. The sum of these details makes the general histological picture in the two conditions very different, but the cardinal differential feature by which the conditions can be separated at a glance is the occurrence in post-vaccinial encephalo-myelitis of perivascular zones of softening of white matter; in poliomyelitis the white matter of the cord is traversed by a variable number of vessels with dark, sharply-defined sleeves of adventitial infiltration, and occasionally contains an extra-adventitial focal group of free cells; in the post-vaccinial cases the white matter is traversed by wide pale zones which encircle vessels and contain relatively few cells.

Histologically the inflammation in ordinary cases of poliomyelitis differs conspicuously from that following vaccination. If post-vaccinial encephalomyelitis is due to a modification of poliomyelitis by vaccinia, the modification has caused anatomically an increase in distribution, an alteration in the relative susceptibility of brain and cord, a sensitization of the white matter and a relative immunity of the grey; and clinically an alteration of symptoms and a freedom from the ordinary sequelæ.

Histological Comparison with Encephalitis Lethargica.

The histological picture in different cases of encephalitis lethargica varies much more widely than in poliomyelitis. In general it can be said that in contrast to poliomyelitis lethargic encephalitis has a greater resemblance to post-vaccinial encephalitis in histological details than in distribution. For purposes of comparison we have examined over 40 cases of encephalitis lethargica, and have analysed the *distribution of lesions* in 26 cases from which a series of portions of tissue were taken for microscopic examination similar to that in Case II. The distribution varies in extent and maximal incidence so greatly in individual cases that it is necessary to give the analysis in some detail. The 26 cases analysed can be divided into two groups: (i) 21 cases in which the basal ganglia, the mid-brain both in its anterior and posterior segments, the pons and the medulla oblongata are all infiltrated, but there are differences in the extent of involvement of the cerebral hemispheres and spinal cord; (ii) 5 cases in which the basal ganglia, the mid-brain in anterior and posterior segments, and the pons and medulla oblongata are not all affected, and there is little or no infiltration of the cerebral hemispheres and spinal cord.

Group (1). In 2 cases, one occurring in 1920 and one in 1921, all the eight segments of the cerebral hemispheres taken according to routine (right and left orbital, prefrontal, central and occipital) and all segments of the spinal cord are affected. These cases are exceptional not only in the wideness of distribution of inflammation but in the magnitude of the leptomeningitis, the very great size of the vascular sleeves throughout and the slightness of extra-adventitial infiltration. In one case, further, vascular sleeves in the white matter are surrounded by zones of closely packed, large polygonal and stellate glial cells with abundant cytoplasm; in this case there is also adventitial infiltration of vessels in some anterior and posterior roots. But although there are numerous large adventitial sleeves in the medulla and all levels of the cortex of the cerebral hemispheres, a little extra-adventitial infiltration of the cortex is only present in one segment of one case. The adventitial infiltration in both cases is so great throughout the central nervous system that it is difficult to determine the site of greatest incidence of inflammation; in one it appears to be in the mid and hind brain, in the other in the spinal cord. These two cases resemble the post-vaccinial in that infiltration was found in every segment taken, but the histological picture is very different.

The remaining 19 cases of this group are most typical of encephalitis lethargica. They differ from the first two, and resemble vaccinial encephalitis, in that meningeal infiltration is in general very slight and focal, and infiltration of the pia in the anterior septum of the cord is slight in comparison with poliomyelitis. The essential difference between the individual cases is the extent to which the spinal cord is involved. In all cases there is little involvement of the cerebral hemispheres in comparison with post-vaccinial encephalitis and even poliomyelitis: in 1 case there is none; in 13 one or more vessels in the medulla of one to four of the eight segments show a single row of glial cells immediately outside the adventitia or, less commonly, a few round-cells within the adventitia; in 5 cases there is a similar slight infiltration of vessels within the cortex of a single segment; in no case are there patches of extra-adventitial infiltration in the cortex or medulla of the convexities, though in 1 case there are numerous adventitial sleeves and patches of extra-adventitial infiltration in the cortex and medulla of the insula. In 3 cases all segments of the cord are infiltrated. In 6 cases infiltrated segments alternate with segments that are free: the free segments are (i) ninth thoracic, (ii) fourth and ninth thoracic, (iii) all thoracic, in two cases, (iv) fourth cervical to second thoracic, (v) thoracic, lower lumbar and sacral. In 2 cases infiltration is not found below the first and the fourth thoracic. In 3 cases it is not found below the second (two cases) and third cervical segments. In 5 cases there is no infiltration of the spinal cord.

In 1 case the upper extremity of the pons is the most severely affected part of the brain and brain-stem. In the remaining 18 the mid-brain is most affected, whilst the lower medulla is least; the affection of the basal ganglia is second in 9 of these, being slightly greater than that of the pons and upper medulla in 5 and much greater in 4; the affection of the pons and upper medulla is second in 9, being greater than that of the basal ganglia. In 2 of the three cases in which the whole cord is involved the affection of the cord is not appreciably less than that of the basal ganglia, pons and medulla; in the remaining 17 cases the cord is obviously less affected.

The posterior root ganglia were examined in 5 of the cases in this group: a small focus of infiltration was found in a thoracic ganglion in 1 case.

Group (2). These 5 examples were in children under thirteen years of age who had been ill for only one to seven days. The infiltration is very slight and strictly limited. In 1 case there is a trace of adventitial infiltration in the medulla of three out of eight cerebral segments and in the cortex of one; there are adventitial sleeves in the posterior corpora quadrigemina, pons and medulla, and a little extra-adventitial infiltration in the pons. In 1 there is a trace of adventitial infiltration in the medulla of one cerebral segment, the left basal ganglia, the posterior corpora quadrigemina and the upper medulla oblongata; and there is one vessel with a more conspicuous sleeve in the pons. In 1 there is a trace of adventitial infiltration in the medulla of one cerebral segment and in the pons, and a greater infiltration of the adventitia of one vessel in the right basal ganglia. In 1 the evidence of inflammation was confined to adventitial infiltration of two vessels in the pons; in 1 to adventitial infiltration of a single vessel in the anterior corpora quadrigemina.

The above analysis shows that it is very exceptional for the inflammation in encephalitis lethargica to be as extensive as in post-vaccinial encephalitis: indeed, it is usually less extensive than in poliomyelitis. As a rule inflammation of the cerebral hemispheres is much less widespread, though in two otherwise exceptional cases it was found in every segment examined as in the vaccinial cases. Extensive infiltration of the spinal cord is less exceptional: all segments of the cord were affected in 5 or 19·2 per cent. of the cases. Infiltration of all segments of the cerebrum and of the spinal cord was only found in the two exceptional cases. The incidence of the inflammation resembles that in vaccinial encephalitis in the following respects. Meningeal infiltration is, except in the two exceptional cases of extensive distribution, slight and focal, and there is little infiltration of the anterior fissure of the cord. In the two segments of cortex in which there was extra-adventitial infiltration the deeper layers were affected. In the basal ganglia the ventral and caudal portions of the optic thalamus, including the pulvinar, are most affected, if not alone affected. The substantia nigra is almost invariably the most severely affected portion of the mid-brain; in Group (1) the grey matter of the aqueduct is as severely affected in 4 cases, but in only 1 case is the infiltration of the substantia nigra relatively slight. The various nuclei infiltrated in post-vaccinial encephalitis are infiltrated in one or other of the cases of encephalitis lethargica. But the differences in incidence are more conspicuous. Inflammation in the cerebral hemispheres is characteristically very slight. Adventitial infiltration, save in the two exceptional cases, is represented by a single row of glial cells immediately outside the adventitia or by a few cells within the adventitia of vessels in the medulla of a few segments and, rarely, in the cortex of a single segment. Extra-adventitial infiltration was only found in the cortex of one segment of 2 cases—in one of the two exceptional cases and in one other. The dorsal portion of the pons is much more affected than the basal, infiltration of the pontine nuclei being in general slight: in 9 cases infiltration of the pontine nuclei is absent; in 9 it is very slight, in 2 it is slight but focal; in 6 there is great infiltration limited to the more dorsal nuclei: in 1 case it is as great and in 2 cases greater than in the substantia nigra, but in no case is it actually as great as in the post-vaccinial cases. Foci of extra-adventitial infiltration in the olives are seldom found and are sparse. With few exceptions the substantia nigra is the most infiltrated or one of the most infiltrated areas in the central nervous system, the infiltration of the spinal cord, even when it affects all segments, being almost invariably much less in amount than in the mid-brain, basal ganglia, pons or upper medulla oblongata. Finally, the white matter is very much less affected than in the cases of post-vaccinial encephalitis: the vessels traversing it may have stout sleeves, and cells immediately outside the adventitia may take a part in the formation of these sleeves, but in only one of the two cases of exceptional distribution are there perivascular zones of infiltration of the white matter, and these perivascular zones are very unlike the zones of softening in the vaccinial cases.

The *histological details* vary in individual cases much more than in poliomyelitis. In general it can be said that in these details encephalitis lethargica resembles post-vaccinial encephalitis more than poliomyelitis does. Vascular engorgement is conspicuous as in post-vaccinial encephalitis and poliomyelitis. The various thrombi found in the post-vaccinial cases occur. Hæmorrhages, which are usually said to be a characteristic feature of this inflammation, are not a special feature of our series. They are always perivascular. In one case they are relatively large and very numerous in one uncus; in another case they are of the size found in post-vaccinial encephalitis and poliomyelitis, but are more numerous throughout the central nervous system. All the cells found in the infiltrations in the post-vaccinial cases are represented. In the formation of vascular sleeves, especially in initial stages, cells immediately outside the adventitia take a considerable share here as in post-vaccinial encephalitis. The disposition of the cells of the extra-adventitial infiltrations within the grey matter is very similar: a perivascular arrangement is usually distinct, unless obscured by wide extension and confluence; the cells are generally scattered diffusely, although occasionally they are gathered into the closely packed focal aggregates that are so common in poliomyelitis; in one case glial cells with elongated oval nuclei are abundant round vessels in the grey matter so as to recall the perivascular infiltration without softening occasionally seen in the white matter in post-vaccinial encephalitis. But these resemblances are not complete. Thrombi are less numerous. Although all the cells found in the infiltrations in the vaccinial cases are found here and the infiltrations are often identical, yet there is a characteristic infiltration in encephalitis lethargica. The characteristic of infiltrations of the adventitia is the predominance of the plasmacytoid cells and large cells with histiocytic nuclei, whilst plasma-cells are more numerous and hyaline cells and neutrophil leucocytes are less numerous than in the vaccinial cases; in the extra-adventitial infiltrations neutrophil leucocytes are less numerous; further, multinuclear giant-cells occasionally occur within or immediately outside the adventitia. There is a great variation in different cases in the size of the sleeves, but in general their size corresponds to the amount of inflammatory reaction; the sleeve is composed of only one or two rows of cells when evidence of general inflammation in the segment is slight, and is massive when it is great. Consequently the sleeves are in general larger than in the post-vaccinial cases and are much larger where the inflammation appears to be as intense. Finally, we have not found in any case the perivascular zones of softening that are so conspicuous in the white matter of post-vaccinial encephalitis. In one of the two cases of exceptionally extensive distribution vessels in the white matter have large sleeves of adventitial infiltration, and outside these is a zone of densely packed large polygonal and stellate cells. This case shows that in encephalitis lethargica there may be a severe perivascular inflammation of the white matter; and such a proliferation of glial cells in the white matter is undoubtedly related to the softening with relatively little cellular proliferation of the post-vaccinial cases, because in two cases of acute disseminated sclerosis we have found both conditions represented. We have, however, found in no case of encephalitis lethargica perivascular zones of softening such as are so characteristic of the post-vaccinial cases.

Encephalitis lethargica, therefore, differs from post-vaccinial encephalitis in extent of distribution. In two exceptional cases, certainly, the extent was similar, infiltration being found as in the post-vaccinial cases in every segment examined; but the general picture in these two cases was entirely different, the inflammation being characterized by great infiltration of the leptomeninges, by massive adventitial sleeves, supplemented in one case by great proliferation of adjacent glial cells, and by little extra-adventitial infiltration of the ordinary kind. In maximal incidence of inflammation it also differs, the sites of election being the mid-brain, especially the substantia nigra, the caudal extremity of the optic thalamus, the dorsal portion of the pons and the cephalic extremity of the medulla oblongata. In histological detail there are many resemblances, but there are many differences. An attempt has been made to enumerate these resemblances and differences, but it would perhaps be simpler to say that we have found no case of encephalitis lethargica that could not quickly be differentiated from the post-vaccinial cases under a low power of the microscope. The most striking differential feature of the post-vaccinial cases is the zone of softening round vessels in the white matter. The great variation in the distribution and the histological details in cases of encephalitis lethargica makes it difficult to contrast the two inflammations concisely; and this of itself is a striking differential point: there is an astonishing similarity in distribution, sites of maximal incidence and histological detail in all seven cases of post-vaccinial encephalo-myelitis.

Histologically it is certainly more likely that post-vaccinial encephalo-myelitis could be caused by the virus of encephalitis lethargica than by the virus of poliomyelitis, and clinically the two conditions have much in common. But if post-vaccinial encephalo-myelitis is caused by the virus of encephalitis lethargica, then the resulting reaction has been so greatly altered by the vaccination as to give a definitely distinct histological picture.

Encephalitis Caused by the Vaccinial Virus.

That vaccinia can cause encephalitis has been demonstrated in the rabbit by Marie (1920) and by Levaditi, Harvier and Nicolau (1922). Marie showed that introduction of vaccine lymph into the brain of the rabbit caused symptoms of encephalitis, a rise in temperature and death between the fifth and eighth day; that the lymph could be recovered from the brain and that the encephalitis could be propagated in series from rabbit to rabbit by inoculation into the central nervous system of a filtered emulsion of either brain or cord. Levaditi and his co-workers found that the vaccine virus had an intermittent neurotropic affinity but could be given a constant neurotropic affinity by numerous alternate passages into the testis and brain. They showed that a meningo-encephalitis can be demonstrated histologically: they described a mononuclear leptomeningitis with perivascular sleeves in the brain substance, and also mentioned an acute polynuclear encephalitis (signes d'encéphalite aigue à polynucleaires) without neuronophagia.

In such sections as we have seen of the brain of rabbits inoculated intracranially with vaccine lymph the meningitis has been more conspicuous than the encephalitis. The infiltration of the pia arachnoid consists chiefly of mononuclear cells with basophil cytoplasm. A few of these cells resemble the small lymphocytes of the blood: the majority are larger cells with relatively abundant cytoplasm; a considerable number of these are large lymphocytes with deeply basophil cytoplasm, but most appear to be large mononuclear leucocytes and endothelial cells. Among these mononuclear cells are scattered granular polymorphonuclear leucocytes, of which most contain fine granules. In the infiltration in the adventitial sleeves surrounding the vessels in the substance of the brain granular leucocytes are extremely rare. In the less intense reactions such infiltration of the leptomeninges and of the adventitia of perforating vessels is alone seen. In the more intense reactions there are areas of serous exudation and of necrosis with nuclear fragmentation in the infiltrated leptomeninges, glial cells in places have proliferated immediately under the pia and sometimes round perforating vessels, and a few perforating vessels close to the pia are surrounded by a zone of serous imbibition; these zones and the serous exudates in the meninges give Weigert's reaction for fibrin. The experimental vaccinial meningo-encephalitis in the rabbit resembles, therefore, histologically human post-vaccinial encephalitis, poliomyelitis and encephalitis lethargica in that it is essentially a non-purulent inflammatory reaction, although granular polymorphonuclear leucocytes occur.

Nervous Complications of Variola.

The virus of vaccinia is closely allied to that of variola (Gordon, 1925), if it is not the identical virus modified by animal passage (Huguenin, 1897; Copeman, 1903; Ledingham, 1925; Winkler, 1925). If, therefore, post-vaccinial encephalomyelitis in man is directly due to vaccination, one would expect encephalomyelitis to occur in cases of human smallpox. Besides delirium or convulsions during the first fever, delirium during the stage of eruption, melancholia and mania many affections of the central nervous system have been recorded in smallpox, although all authorities agree upon their relative rarity; thus Spiller (1903) says that Schamberg had observed only 7 instances of paralysis in 2800 consecutive cases. Some of the nervous complications are clearly secondary, for instance the purulent meningitis of Wagner (1872), and the streptococcal meningitis and myelitis of Auché and Hobbs (1894); in this category must also be placed the case of encephalomyelitis of Oettinger and Marinesco (1895), although the illustrations of their streptococci are not convincing. In the majority of cases the patients survived and the nature of the infection was unknown; in a few the infection was proved by necropsy to be non-pyogenic.

In one group of these cases *disturbances of articulation* were observed either alone or combined with disturbances of muscles supplied by bulbar nerves. Gubler and Laborde (1871) mention two instances: (1) a young female was unable to articulate when the eruption had just commenced, but began to recover speech at the stage of full suppuration of a confluent smallpox; (2) a young male could scarcely articulate on the second day after eruption, but recovered thirteen or fourteen days later. Guttstadt (1872) had seen three examples of disturbances of speech: the most striking was that of a man of twenty who could not speak on recovering consciousness during the stage of desiccation of a confluent smallpox, but gradually learned to speak again. Wohlrab (1872) observed alteration in speech in a man of twenty on his recovery from stupor four days after the commencement of desiccation; slight disturbance in speech was still present three months later. In the third case of Combemale (1892) a man of twenty-two had intermittent disturbances of speech during the eruption and recovered during desiccation. In Combemale's first case a slow, nasal speech was noticed in a woman of twenty on the eleventh day of illness and eighth after eruption; this was associated with a convergent squint and ataxic movements of the tongue and cheeks; these abnormalities were still present when the last observation was made a month later. In the fourth case of Aldrich (1904) a boy of seven had violent convulsions on the second day of illness and was stuporose next day. On the fourth morning a discrete eruption appeared. For three months after recovering consciousness he did not speak; but he then learned readily and in six months could speak almost as fluently as before.

In a second group were *disturbances of articulation associated with disturbances of limb movements.* Westphal (1872) described three such cases, and a fourth (Case 3) which more probably belongs to the first group. (1) On the day of onset of illness, two days before the eruption, a woman of forty-seven could only utter three words; next day she could not stand. Two months after the onset the speech was difficult, nasal, scanning, without modulation and often unintelligible; the face was peculiarly expressionless; there were tremors of the head suggesting paralysis agitans, and ataxia of arms and legs; sensation was unimpaired; the patient was emotional. Five months later there was slight improvement of speech and gait. (2) A man of twenty-eight was comatose during the first two days of illness, began to lose power of speech just as the pocks were fully developed and was unable to use his hands. Later when he got up he could not stand or walk. He gradually learned to walk and use his hands, but seven weeks later the speech resembled that in the first case, separate consecutive movements of the fingers as in playing the piano were slow and clumsy, the gait was stiff with short steps, memory was greatly impaired and the patient was very emotional; sensation was unimpaired. After five months there was no appreciable change. (3) A man of twenty-four was unconscious during the initial eight days of varioloid. A disturbance of speech similar to that in the other two cases followed. Owing to a congenital deformity of his arms and legs it was not possible to be certain of any alteration in the movements of the limbs. (4) A woman of forty became hoarse on the third day of variola, a day before eruption; a fortnight later the speech resembled that of a deaf mute and the arms were ataxic. Six months later the speech was as in the other cases, there was some subjective difficulty in swallowing and the movements of the fingers, especially of the right hand, were slow and clumsy as in the second case; true ataxia was now absent. Whipham and Myers (1886) described two very similar cases. (1) A female of thirty-nine was unable to speak or put out her tongue and had unequal pupils when seen on the fourth day of the rash. Next day she was unconscious. When consciousness was recovered, on the sixteenth day of rash, her speech was unintelligible and she was unable to move her limbs freely or to walk unaided. When last seen, seven years later, she could walk properly, but her articulation was still almost unintelligible and the movements of her arms were weak and incoordinated. (2) The smallpox started with mania, and the patient, a woman of thirty-eight, made futile efforts to speak and lost almost completely power of moving her limbs. She began to recover a week later, but after four years her articulation was still difficult, thick and jerky, and her gait ataxic. In the second case of Combemale (1892) there was inability to speak, associated with increasing weakness of the pharynx and palate, on the third day of a rash which became confluent; paraplegia occurred suddenly during convalescence but disappeared five days later. Spiller (1903) describes an observation of Schamberg in which paresis of arms and legs, stupor, difficulty in swallowing and great difficulty in articulation appeared in the initial stages; paralysis became almost complete, but when the patient was discharged all signs had disappeared except a scanning speech. Aldrich (1904) published two examples. (1) A boy of thirteen, when convalescent on the fifteenth day from the start of a mild smallpox, became stuporose, complained of headache and became aphasic, whilst the temperature rose. Later he had difficulty in swallowing and his speech was hesitating; a fortnight later he could not stand. Subsequently his gait was ataxic. Five months after the commencement of illness the walk was ataxic, the speech was halting and blurred, there was athetosis of the right hand and the patient was emotional and subject to violent fits of passion. A cerebral lesion was diagnosed. (2) A woman became delirious on the third day after eruption. Shortly after this she was aphasic, had difficulty in swallowing, lay helpless in bed and lost control of her sphincters; the deep reflexes were absent. Speech slowly improved after three weeks; the paralyses were followed by conspicuous ataxia of gait, and the patient looked and acted like an imbecile. After two months there was rapid improvement. At the final examination the gait was slightly ataxic, the speech slow and scanning and the knee-jerks perhaps slightly increased. Kleineberger (1913) examined a woman of thirty-one who at the end of her school days had had sudden motor aphasia and paralysis of the right arm and leg, about four weeks after the commencement of a mild attack of smallpox. The aphasia disappeared entirely and the paralysis partially. Six or seven years later a rapid fine tremor appeared in the right arm and spread over the body. Later, signs and symptoms developed that pointed to disturbance of the endocrine system, and these Kleineberger attributed to hydrocephalus following encephalo-myelitis. Sottas (1892) published an example which ultimately resembled disseminated sclerosis very closely. A lad of eighteen had a discrete smallpox with initial symptoms that were predominantly nervous and so severe that meningitis was diagnosed. He became semi-comatose and was generally paralysed. Later the speech resembled that of bulbar paralysis, there were fibrillar movements of the tongue and slight nystagmus, whilst the paralysis of the limbs gradually gave way to inco-ordination, voluntary tremor, spasticity, pes equinus and exaggerated reflexes. Nine months later the trembling of the tongue had disappeared, but the other signs persisted and the patient was emotional and subject to violent fits of temper.

In a third group *paralysis of the limbs* alone was observed. Leroy d'Étiolles (1856) had seen variola twice complicated by paraplegia: (1) paraplegia appeared during the incubation period and disappeared when the exanthem cleared up; (2) paraplegia suddenly appeared during the period of desquamation. Gubler and Laborde (1871) observed in a patient who had recovered from a confluent smallpox a paralysis of the legs that was at first complete, but which became incomplete and persisted for more than three months. Spiller (1903) mentions a case of Schamberg's in which a young negro who had gangrene of the genitalia complicating smallpox developed after ten weeks' partial loss of power in the arms and legs; the paresis persisted until he was discharged. A case of Damaschino (1871) suggests *poliomyelitis*. A boy of two and a half was found to be unable to walk when an attempt was made to get him up on convalescence from discrete smallpox in the month of July. The paraplegia improved greatly after several months, especially on the right side, but six months later it was still present, when pneumonia complicating measles caused death.

Finally there is a group of cases in which *paralysis of limbs was accompanied by paralysis of bladder and rectum.* Several of these cases were called examples of Landry's paralysis. In a case published by Bernhardt (1871) and Guttstadt (1872) a man of twenty-eight who had been ill for eight days with a discrete smallpox was going to be discharged when he complained of weakness in the limbs and the right eye and of numbness of the right hand. Loss of power in the right arm increased daily and the legs became paralysed. There was incontinence of urine on the twenty-first day after the initial rigor, and death occurred three days later. Westphal (1874) published two examples. (1) Eleven days after the eruption of varioloid, during desiccation, a male of thirty-two had paralysis of the bladder. Next day the left leg was paralysed and there was incontinence of fæces. Next day the right leg was paralysed. Inflammation of the bladder, a pressure ulcer and sepsis followed, and death occurred five weeks after the eruption. (2) Three days after the eruption of varioloid a man of twenty-two could not move his legs and had incontinence of urine. He became gradually better but died from perforation of the appendix. Spiller (1903) published two cases. (1) A woman of nineteen who had had severe smallpox was progressing well when in the third week she was unable to move her legs in bed; control of the bladder and rectum was lost and sensation in the legs was impaired. Within a few days there was partial restoration of motion in the lower limbs, but severe diarrhœa led to death at the end of eight or nine weeks. (2) A man of thirty-eight on the eighth day of a scanty rash lost power in his legs; the bladder was paralysed and the bowels constipated. Three days later movement of the legs was greater but the knee-jerks were absent. Catheterization had to be continued. Incontinence of urine and fæces and much diarrhœa appeared four weeks after the commencement of the rash, and ten days later the patient died. In the case of Eichorst (1913) a man of forty on the fifteenth day of illness and eleventh of rash, when the pustules were beginning to desiccate, suddenly felt during the night great weakness in both legs. In the morning movement of the toes was alone possible, the tendon reflexes were absent, the bladder and rectum were incontinent but skin sensation was unimpaired. Next day paralysis of the legs was complete. On the eighteenth day of illness increasing coma and shallow breathing were followed by death. The cases of Auché and Hobbs (1894), and of Oettinger and Marinesco (1895) fall clinically into this group, but in both the infection of the central nervous system was found to be streptococcal and, therefore, definitely secondary.

References to clinical histories of a like kind are given in the papers by the authors quoted, but very few *necropsies* are recorded. Some of these refer to secondary pyogenic infections (Wagner, 1872; Auché and Hobbs, 1894; Oettinger and Marinesco, 1895). Records of non-purulent inflammation are very scanty. Wagner (1872) in an examination of about thirty brains found an area of fresh red softening of the size of a walnut in the right occipital lobe of a woman of twenty-eight. We have found 7 cases in which clinical histories and necropsies are given; the clinical histories have been summarized above.

Damaschino (1871), in his case that resembled clinically *poliomyelitis*, found at necropsy six months later in the lumbar region of the spinal cord an area of softening in a left anterior horn, loss of ganglion cells in the grey matter and of nerve-fibres in the grey and white matter, a few granule cells in adventitial sheaths and some gliosis in the white matter; he found similar changes of less degree in the thoracic and cervical regions, and a slight atrophy of fibres in the pyramids of the medulla oblongata. The other necropsies were upon cases in the group of *paralysis of limbs and of bladder and rectum.* Ponfick in 1871 in the case published by both Bernhardt (1871) and Guttstadt (1872) made a microscopic examination of the spinal cord, medulla oblongata, basal ganglia, nerve-roots, nerves and muscles, and found nothing abnormal. Westphal examined the cord in his two cases published in 1874. In his first case in sections of the lower lumbar region of the cord, examined when fresh, granule cells were found in the vascular sheaths and masses of granule cells in the anterior and posterior horns. When the cord had been fixed in Müller's fluid bright yellow foci of infiltration were conspicuous in the grey and white matter. Still more foci were seen in stained sections. These consisted of fat-granule cells, which usually formed a ring round engorged vessels and lay in both grey and white matter.

A plate is appended in which the bright yellow areas seen in the Müller sections are depicted of natural size in black in a long series of segments of the cord: many strands of infiltration, often very broad, are seen radiating from the grey matter across the white matter of the lateral columns and less often of the anterior and posterior columns. The lumbar cord was most severely affected; the affection then decreased but became severe again in the upper thoracic region to decrease in the cervical. The grey matter was more affected than the white. He could not be certain that any ganglion cells had been lost. In his second patient, who died of appendicitis when recovering, the changes were essentially similar. The grey matter was only slightly affected, excepting an area of softening in the thoracic region; the lateral were the most affected of the white columns, and were least involved in the cervical region. He named the condition "spotted or disseminated myelitis": "Die fleckweise oder disseminierte Myelitis." In both cases of paralysis of limbs, rectum and bladder described by Spiller (1903) the spinal cord was examined. In the first case "nothing distinctly abnormal could be detected." In the second the vessels in the anterior horns were congested. The methods of Marchi and Weigert showed areas of degeneration in the grey matter that were almost confined to the anterior horns. These areas were most conspicuous in the lumbar region and were present in the mid-thoracic cord, but only one was found in an anterior horn in the cervical region. They showed masses of fat-granule cells and a perivascular infiltration. There was a considerable amount of degeneration of scattered fibres in the white matter of the mid-thoracic and cervical regions but only a trace in the lumbar. The nerve-cells were not greatly altered, but tigrolysis, displacement of nuclei and loss of dendrons were observed in the lumbar and cervical regions. Spiller regarded the changes as those of an anterior poliomyelitis. In the case of Eichorst (1913) the brain and spinal cord looked normal to the naked eye. The spinal cord was examined microscopically and was found to be beset in its full length with areas of infiltration. The infiltration was greatest in the grey matter and in the anterior horns but was seldom confined thereto, extending sometimes more sometimes less into the white matter. Both grey and white matter were most affected in the lumbar region; the infiltration decreased in ascending segments and became more and more confined to the anterior horns. In the lumbar cord the infiltrated areas in the white matter could be seen with the naked eye; in an illustration of a stained section magnified seven diameters the conspicuous strands and patches of infiltration in the lateral and anterior columns are remarkably like the zones of softening in our cases of post-vaccinial myelitis but are densely cellular. Most of the areas of infiltration in the grey matter were only a continuation of those in the white. There were hæmorrhages in the white matter of the lumbar cord but not in the grey. The pia showed hyperæmia rather than inflammation, but was infiltrated in the lumbar region. The infiltrations consisted almost exclusively of mononuclear-round cells, usually packed closely together. The cells lay not infrequently in the adventitia or both in the adventitia and in a narrow zone immediately outside, but more often in a broad extra-adventitial zone. As in some of our cases of post-vaccinial encephalitis there was in several places a zone of infiltration of the white matter on either side of the anterior septum; this is shown in an illustration, and the septum is not infiltrated. The ganglion cells in the anterior cornua appeared to be preserved although closely surrounded by infiltrating cells. The white matter was free from degeneration between the areas of infiltration. There was neither hæmorrhage nor infiltration in the spinal roots. No bacteria were recognized in sections.

Among the complications, therefore, of smallpox recorded in the literature there are many affections of the central nervous system that are clinically unlike pyogenic infections or have been proved microscopically to be non-pyogenic. They have complicated either mild or confluent smallpox, have arisen at all stages from the prodromal to convalescence, and have affected children as well as adults. In some of these disturbance of articulation was alone observed, and this tended to clear up completely. The majority suggest a more disseminated inflammation; many, indeed, resembled disseminated sclerosis closely, but differed in that the condition so far from progressing tended to improve. Partial or complete recovery was the rule, and explains the absence of necropsies. In this respect they resembled post-vaccinial encephalitis, although they differed in so frequently leaving permanent disturbances that have not been recorded after vaccination. In another group paraplegias have occurred that have cleared up when the patients have been observed for any length of time. A paraplegia that cleared up only in part was recorded by Damaschino (1871); but this was probably an example of true poliomyelitis as a complication: the patient was a young child, the illness commenced in July, and the microscopic changes described in the cord agree with healing poliomyelitis. In a small group of 6 cases paraplegia was combined with paralysis of the bladder and rectum. In 1 example death was caused by appendicitis when the condition was improving; in the remainder death was directly or indirectly due to the paralyses. These cases, therefore, bear considerable resemblance to the fatal cases of post-vaccinial encephalomyelitis. In 1 (Bernhardt 1871 and Guttstadt 1872) no change was found microscopically in brain, cord or nerves; again, in 1 of the two cases of Spiller (1903) no change was recognized microscopically in the spinal cord. But in the remaining 4 cases a microscopic examination confined to the spinal cord showed a widely disseminated myelitis of non-purulent type. The lumbar cord was more affected than the cervical; little destruction of ganglion cells was found; the grey matter was implicated more than the white, but the white matter in the two cases of Westphal (1874) and the case of Eichorst (1913) was traversed by conspicuous perivascular bands of infiltration. These bands resembled in prominence and distribution the zones of perivascular softening in post-vaccinial myelitis, but were more densely cellular. Eichorst, whose description is most detailed, described an infiltration round the anterior septum similar to that in post-vaccinial myelitis, and also drew attention to the relative insignificance of the meningeal infiltration.

Specific Lesions in Internal Organs in Vaccinia and Variola.

The presence of lesions specific of vaccinia or variola within the internal organs would have brought evidence in favour of the affection of the central nervous system being vaccinial, though their absence does not exclude such an infection if the nervous system was specially susceptible or the virus specially neurotropic. That specific focal lesions may be widely distributed throughout the internal organs in general vaccinia in the rabbit appears to have been proved by Captain Douglas, who has kindly shown us microscopic sections from experiments, details of which he hopes shortly to publish. Weigert (1874) described in the liver, spleen, kidneys and lymphatic glands of subjects who had died from smallpox miliary lesions that he considered similar to the pocks in the skin, but he described zooglia-like heaps of micro-organisms in their centres. Roger and Weil (1900) in describing the cells that infiltrate such foci in the liver make no mention of micro-organisms. Chiari (1886, 1889) described areas of infiltration in the interstitial tissue of the testicle that became necrosed centrally and extending in size involved the epithelium of the seminal tubules, finally to heal and form small scars. The areas were seen with the naked eye as pale areas up to the size of a pea. He called the condition "orchitis variolosa." Chiari (1893) also described very similar, non-purulent, focal areas of infiltration and central necrosis, up to the size of a pea, in the bone-marrow, and called this condition "osteomyelitis variolosa." In view of these findings it is unfortunate that no microscopic examination was made of the focal necroses in the liver in Case III. In all the microscopic examinations of internal organs that were made (p. 196) nothing in the nature of specific lesions was found.

EXPERIMENTAL INVESTIGATION.

I. *Experiments made by Dr. Paul Fildes.*

(1) *Material from Case II.*

The material was placed at the necropsy in 20 per cent. glycerine and consisted of (1) a portion of cornu Ammonis, (2) the fifth segment of spinal cord, (3) lymphatic glands from left axilla and (4) one of the vaccinated areas.

Expt. 1.—A rabbit inoculated intra-testicularly on Dec. 8, 1922, with an emulsion of axillary gland was killed on Dec. 15. The testicle was found to be greatly swollen and œdematous.

Expt. 2.—A rabbit inoculated intra-dermically on Dec. 8, 1922, with the same emulsion showed no change on Dec. 15 and was vaccinated on the back with fluid from the testicle of rabbit No. 1. A few papules appeared on the back on Dec. 19. No more papules Dec. 20; no abnormality Dec. 22, 27 and Jan. 4, 1923.

Expt. 3.—A rabbit inoculated in the sub-cerebellar cistern and peritoneum on Dec. 8, 1922, with emulsion of axillary gland showed no change on Dec. 20, 22, 27, Jan. 4, 1923, and up to Nov. 30, 1923, when it was killed.

Expt. 4.—A rabbit inoculated intra-cutaneously on Dec. 8, 1922, with emulsion of spinal cord showed no change on Dec. 18, 20, 22, 27 and Jan. 1, 1923.

Expt. 5.—Inoculation of the right cornea of a rabbit by Mr. Humphrey Neame on Dec. 11, 1922, with an emulsion of cornu Ammonis caused an ulcer and conjunctivitis on Dec 18, or possibly earlier. The condition was unchanged and vesicles were absent on Dec. 20 and 22; the ulcer had healed with resulting opacity on Dec. 27; no further change on Jan. 4 and 29, 1923.

Expt. 6.—A rabbit inoculated in the sub-cerebellar cistern on Dec. 8, 1922, with emulsion of spinal cord appeared out-of-sorts on Dec. 12, and was killed with coal-gas on Dec. 13.

Necropsy showed a pale yellow nodule (0·3 cm. diam.), with narrow hæmorrhagic border, in the calamus scriptorius. Histologically this was found to be an abscess, whilst fibrino-purulent lepto-meningitis covered the brain and cord, and pus filled the cerebral ventricles, the iter and the central canal in some of the upper segments of the cord. The exudates contained Gram-positive cocci and diplococci, and Gram-negative coliform bacilli.

(The posterior part of the cerebral hemispheres, the posterior extremity of the cerebellum with subjacent medulla, and the fifth to ninth cervical segments were placed at necropsy in 20 per cent. glycerine.)

Expt. 7.—A rabbit inoculated through the frontal bone on Dec. 27, 1922, with emulsion of the brain from rabbit Expt. 6 was found dead next day.

Expt. 8.—Another rabbit similarly inoculated on Dec. 27, 1922, appeared well on Dec. 29 and Jan. 1, 1923, and was killed with coal-gas on Jan. 13.

Necropsy.—A creamy nodule (1 cm. diam.) in the pericranium at the site of inoculation showed microscopically an infiltration with leucocytes and lymphocytes and a formation of trabeculæ of coarse-fibred bone. No microscopic abnormality was found in complete segments at five levels of the brain and brain-stem and at seven levels of the spinal cord.

(2) *Material from Case III.*

The material was placed at the necropsy in 20 per cent. glycerine, and consisted of the third, fourth, seventh and part of the fifth cervical segments of the spinal cord.

Expt. 1.—A rabbit vaccinated inside the right ear and on a sulphided area on the back on Dec. 18, 1922, with emulsion of the seventh cervical segment showed no change on Dec. 20, 22, 27 and up to Nov. 30, 1923, when it was killed.

Expt. 2.—A rabbit similarly vaccinated on Dec. 21, 1922, with emulsion of the third cervical segment showed no change on Dec. 22, 27, Jan. 4, 1923, and up to Nov. 11, 1923, when it was killed.

Expt. 3.—A rabbit inoculated intra-testicularly on Dec. 18, 1922, with emulsion of the seventh cervical segment showed no change on Dec. 20, 22, 27, 28, Jan. 4, 1923, and up to April 3, 1923, when it was killed.

Expt. 4.—A rabbit inoculated through the frontal bone on Dec. 18, 1922, with emulsion of the seventh cervical segment, was found dead next day.

Expt. 5.—A rabbit inoculated on Dec. 18, 1922, as in the previous experiment, remained well until Mar. 21, 1923, and was then killed.

Expt. 6.—A rabbit inoculated on Dec. 18, 1922, as in Expts. 4 and 5, remained well until Jan. 13, 1923, and was then killed with coal-gas.

Necropsy.—No wound was visible in the calvaria or brain. No microscopic abnormality was detected in complete segments at five levels of the brain and brain-stem and at seven levels of the spinal cord.

Results of Dr. Fildes's Experiments.

With material from Case II the presence of vaccinial virus was demonstrated in the left axillary glands.

No clinical nor histological evidence of encephalitis followed intracerebral inoculation of emulsions of these glands or of spinal cord, nor corneal inoculation of cornu Ammonis.

With material from Case III the results were all negative.

II. Experiments made by Dr. James McIntosh.

A. Intracerebral Inoculation.

(1) *Material from Case III.*

Pieces of the third to fifth and the seventh cervical segments of the spinal cord received in 20 per cent. glycerine were washed in saline, and about 5 gm. were emulsified in 20 c.c. of saline.

Under an anæsthetic the right frontal bone just to the right of the middle line was drilled, and 0·5 c.c. of the emulsion was injected by means of a syringe and needle into the brain of two *Macacus rhesus* monkeys and two rabbits. In each case 5 c.c. of the emulsion was also inoculated subcutaneously.

Expt. 1*a* (137, 1922). *Macacus rhesus*, small female.

22 . 12 . 22.	Intracerebral and subcutaneous inoculation.
23 . 12 . 22.	Quite fit and active. Temp. 102·4° F.
27 . 12 . 22.	Seems excited; perhaps some inco-ordination of arms; slight diarrhœa. T. 102·6°.
28 . 12 . 22.	Condition similar. T. 101·8°.
30 . 12 . 22.	,, ,, T. 102·2°.
1 . 1 . 23.	No diarrhœa, but seems weaker and inco-ordination more pronounced. T. 101·2°.
3 . 1 . 23.	Right wrist-drop; difficulty in climbing cage. T. 102·2°.
4 . 1 . 23.	Can now hold food in left hand only. T. 100·4°.
5 . 1 . 23.	Killed with coal-gas. T. 99·4°.

Necropsy.—Catarrhal enteritis and colitis were found. A trephine puncture (0·1 cm. diam.) lay in the right frontal bone, 2 cm. above the right orbital margin and 1 cm. from the mid-line. The only abnormalities detected with the naked eye in the brain and cord were two bright red petechiæ beneath the callosal gyrus in the right frontal lobe.

Microscopic sections were made of (1) a vertical section through the right frontal lobe. to include the above petechiæ, (2) through the basal ganglia, (3) the anterior corpora quadrigemina and cornu Ammonis, (4) the pons at the level of the fifth cranial roots, (5) the medulla oblongata, (6) cervical segment II, (7) C VIII, (8) Th II, (9) L IV.

In section (1), in the callosal gyrus and passing obliquely downwards and outwards, was a streak of hæmorrhage. This was surrounded by a broad zone of proliferated glial cells, of which most were fat-granule cells. Some of the vessels in this zone had a sleeve of lymphocytoid cells. In the leptomeninges of this section there was a slight infiltration with endothelial cells and occasional granular leucocytes. In no other section was there any abnormality, except small hæmorrhages in the junction of the right posterior and anterior cornua of the eighth cervical segment of the cord.

The streak evidently corresponded to the track of the inoculating needle.

(The parietal lobes with basal ganglia, the anterior part of the pons, and cord segments C IV to VII, Th V to IX were placed at the necropsy in 33 per cent. glycerine.)

Expt. 1*b* (137, 1922). *Macacus rhesus*, small male.

22 . 12 . 22. Intracerebral and subcutaneous inoculation, as in 1*a*.
23 . 12 . 22. Complete recovery from operation. T. 101·8°.
27 . 12 . 22. Perfectly well. T. 101·0°.
28 . 12 . 22. „ T. 102·0°.
30 . 12 . 22. „ T. 99·2°.
1 . 1 . 23. „ T. 100·8°.
9 . 1 . 23. Slight indication of inco-ordination in right wrist; animal disinclined to move.
10 . 1 . 23. Condition similar.
11 . 1 . 23. Seems better. T. 100·4°.
12 . 1 . 23. Perfectly well. T. 100·0°.
The animal was under observation until 3 . 2 . 23 and showed no further change.

Expt. 1*c* (137, 1922). Two rabbits, *A* and *B*.

22 . 12 . 22. Intracerebral and subcutaneous inoculation, as in 1*a*. Complete recovery soon after operation.
23 . 12 . 22. Rabbit *A* found dead in morning from cerebral hæmorrhage. Rabbit *B* appears well. T. 99·0°.
27 . 12 . 22. Rabbit *B*: restless and excited; no paralysis. T. 105·0°.
28 . 12 . 22. „ „ „ T. 105·5°.
29 . 12 . 22. „ „ „ T. 103·4°.

Killed with coal-gas. Brain and cord normal in appearance; no œdema, hæmorrhage nor pus. Slight effusion into both pleuræ. Cultures sterile.

Expt. 2 (6, 1923). Young *Macacus rhesus* monkey and two rabbits *A* and *B*.

8 . 1 . 23. Intracerebral inoculation of 0·75 c.c. of emulsion of brain of monkey of Expt. 1*a*.
Monkey. 9 . 1 . 23. Normal. T. 102·8°.
10 . 1 . 23. Excited; limbs trembling; some weakness of arms. T. 104·2°.
11 . 1 . 23. Quieter. T. 102·0°.
12 . 1 . 23. Perfectly well. T. 101·8°.
13 . 1 . 23 to 20 . 1 . 23. No abnormal symptoms.
Rabbit A. 9 . 1 . 23. Found dead in morning.
Rabbit B. 12 . 1 . 23. Died after showing a slight rise of temperature.

Necropsy, Rabbit B.—Brain normal to naked eye, but a distinct non-purulent meningo-encephalitis found on histological examination.

Expt. 3 (10, 1923). Two rabbits, *A* and *B*.

12 . 1 . 23. Intracerebral inoculation with 0·25 c.c. of brain emulsion from monkey of Expt. 1*a*.
13 . 1 . 23. T.: *A* 102·4°. *B* 103·8°.
15 . 1 . 23. T.: *A* 99·4°. *B* 100·8°.
16 . 1 . 23. T.: *A* 102·0°. *B* 100·2°.
17 . 1 . 23. Rabbit *B* eats little and is disinclined to move. T.: *A* 102·0°. *B* 103·0°.
18 . 1 . 23. „ „ T.: *A* 102·8°. *B* 105·2°.
19 . 1 . 23. „ „ T.: *A* 102·4°. *B* 105·2°.
20 . 1 . 23. „ „ T.: *A* 102·6°. *B* 106·4°.
22 . 1 . 23. Rabbit *B* obviously ill; killed. T.: *A* 102·2°. *B* 104·4°.

The brain of Rabbit *B* appeared to the naked eye to be perfectly normal; microscopically no change of significance was found.

Expt. 4 (23, 1923). Two male rabbits.

22 . 1 . 23. Inoculation into right testicles of emulsion of brain from rabbit *B* of Expt. 3.
23 . 1 . 23. Slight enlargement of testicles.
24 . 1 . 23. " "
25 . 1 . 23. Enlargement now less.
26 . 1 . 23. Testicles normal.
Animals under observation until 5 . 2 . 23 showed no change.

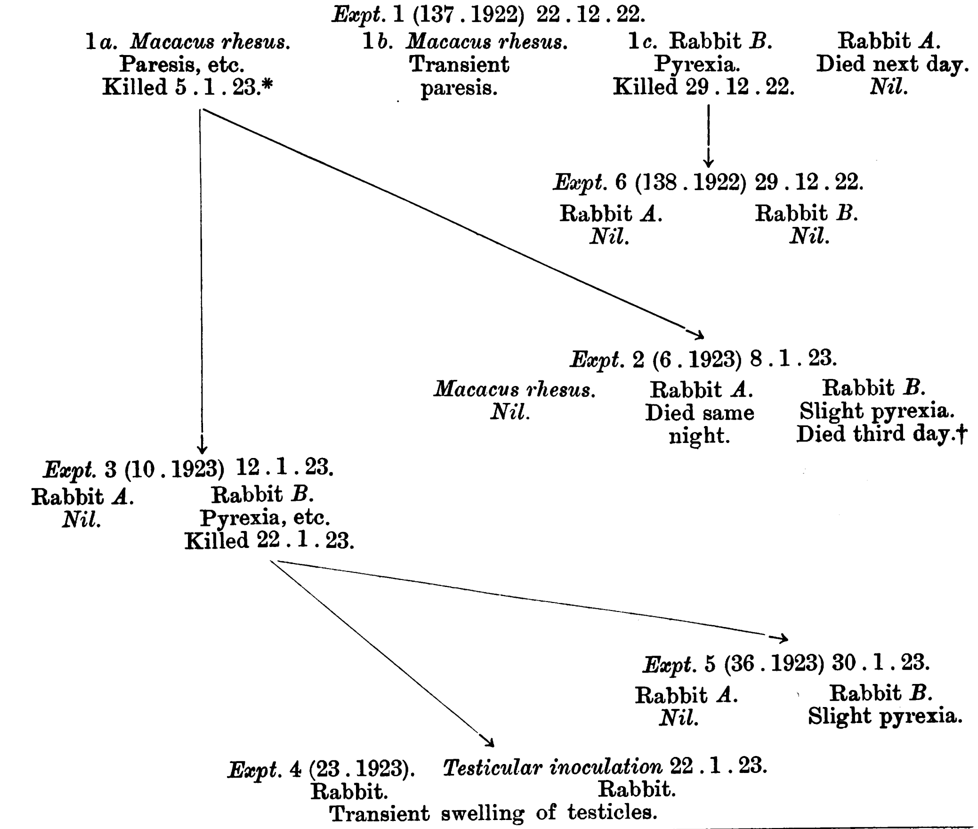
Expt. 5 (36, 1923). Two rabbits, *A* and *B*.

30 . 1 . 23. Intracerebral inoculation with emulsion of brain from rabbit *B* of Expt. 3. Rabbit *B* showed a slight rise of temperature for a few days after the inoculation; otherwise the animals developed no abnormal symptoms.

Expt. 6 (138, 1922). Two rabbits, *A* and *B*.

29 . 12 . 22. Intracerebral inoculation with 0·25 c.c. of emulsion of brain from rabbit *B* of Expt. 1c.
30 . 12 . 22. Both rabbits perfectly well. T.: *A* 103·6°. *B* 103·8°.
1 . 1 . 23. " " T.: *A* 102·6°. *B* 101·4°.
2 . 1 . 23. " " T.: *A* 103·0°. *B* 101·4°.
No significant change was subsequently noted, and the experiment was discontinued.

CHART.—*Intracerebral Inoculation; Passage Experiments; Material from Case III.*



* Non-purulent meningo-encephalitis in track of needle.
† Non-purulent meningo-encephalitis.

(2) *Material from Case IV (convalescent).*

The material consisted of the distal halves of the third and fourth segments of lumbar spinal cord, which had been placed at the necropsy in 33 per cent. glycerine. After thorough washing in normal saline about 1 gm. was emulsified in 10 c.c. of saline.

Expt. 1 (6 and 7, 1922). Small *Macacus rhesus* and two rabbits.
Intracerebral inoculation of 0·5 c.c. of emulsion.
Next day all three animals had recovered completely.
Observed for some weeks they showed no abnormalities.

(3) *Material from Case V.**

The brain in this case was received in a fresh condition. Pieces were removed and placed, some in formaldehyde solution and others in 33 per cent. glycerine. Emulsions were made of 5 gm. of material to 20 c.c. of saline.

Expt. 1*a* (100, 1923). *Macacus rhesus* monkey.

11 . 10 . 23.	Right frontal bone drilled immediately to right of mid-line, under anæsthesia. Subdural injection with syringe of 0·5 c.c. of an emulsion of material from the right and left basal ganglia, the cortex and the lower end of the medulla oblongata. Simultaneous subcutaneous injection of 5 c.c. of the emulsion.
12 . 10 . 23.	Animal active and eating well. T. 101·2°.
13 . 10 . 23.	" " T. 102·0°.
15 . 10 . 23.	Less active; doubtful weakness of hind limbs; slight diarrhœa. T. 102·6°.
16 . 10 . 23.	Distinct weakness in legs. T. 102·8°.
17 . 10 . 23.	" " T. 102·2°.
18 . 10 . 23.	" " T. 102·4°.
19 . 10 . 23.	Animal completely recovered. T. 101·8°.
22 . 10 . 23.	" " T. 101·8°.

Expt. 1*b* (100, 1923). Three rabbits.

11 . 10 . 23.	Intracerebral inoculation with 0·25 c.c. of the same emulsion.
	The rabbits were under observation for several weeks; no abnormal signs developed and the temperatures remained normal.

Necropsies.—Subsequent histological examination showed no abnormalities.

(4) *Material from Case VI.**

Pieces of brain removed at necropsy were placed directly in 33 per cent. glycerine.

Expt. 1*a* (102, 1923). Small *Macacus rhesus* monkey.

22 . 10 . 23.	Intracerebral inoculation of 0·5 c.c. of an emulsion of portions of the basal ganglia and cortex in normal saline.
23 . 10 . 23.	Monkey fit and well. T. 101·4°.
24 . 10 . 23.	" " T. 102·0°.
25 . 10 . 23.	" " T. 102·6°.
26 . 10 . 23.	" " T. 102·4°.
27 . 10 . 23.	" " T. 101·8°.
1 . 11 . 23.	" " T. 102·2°.

Expt. 1*b* (102, 1923). Two rabbits, *A* and *B*.

22 . 10 . 23.	Intracerebral inoculation of 0·25 c.c. of the same emulsion.
23 . 10 . 23.	Both completely recovered from operation. T.: *A* 102·0°. *B* 101·8°.
24 . 10 . 23.	" " T.: *A* 100·8°. *B* 101·4°.
25 . 10 . 23.	Rabbit *B* showed slight lassitude. T.: *A* 101·2°. *B* 103·0°.
26 . 10 . 23.	Conditions unchanged. T.: *A* 101·8°. *B* 103·2°.
27 . 10 . 23.	" " T.: *A* 102·4°. *B* 103·8°.
28 . 10 . 23.	" " T.: *A* 102·8°. *B* 103·0°.
29 . 10 . 23.	" " Rabbit *B* killed. T.: *A* 102·2°.
30 . 10 . 23.	Rabbit *A* fit and well. T.: *A* 102·6°.
31 . 10 . 23.	" " T.: *A* 102·4°.
1 . 1 . 24.	" " T.: *A* 101·6°.

Necropsy, Rabbit B.—Histological examination of the brain showed a well-marked non-purulent meningitis.

* Experiments with material from this case were made on behalf of the Ministry of Health.

Expt. 2 (107, 1923). Two rabbits, *A* and *B*.

29 . 10 . 23. Intracerebral inoculation with an emulsion of brain of rabbit *B* of Expt. 1*b*.
30 . 10 . 23. Both rabbits appear to have recovered from operation. T.: *A* 104·2°. *B* 102·8°.
31 . 10 . 23. Both normal. T.: *A* 102·8°. *B* 102·4°.
1 . 11 . 23. „ T.: *A* 102·6°. *B* 101·8°.
9 . 11 . 23. No change in condition and no rise in temperature since last observation. T.: *A* 102·0°. *B* 101·4°.

B. Allergic Experiments.

In collaboration with Dr. Blaxall allergic experiments were made for the Vaccine Committee of the Ministry of Health with material from Cases III and IV. The results of these experiments, which are to be reported elsewhere, were negative with one doubtful exception.

C. Demonstration of Vaccinia Virus in Encephalitic Brains.

Attempts to raise vaccinia virus from Cases V and VI were successful, both by the intradermic method as suggested by Dr. Blaxall and by the intratesticular method.

Expt. 1 (104, 1923). Rabbits; intradermic method.

25 . 10 . 23. Two small rabbits were inoculated by scarification of the shaved flanks, one with brain emulsion from Case V, the other with brain emulsion from Case VI.
26 . 10 . 23. Slight local reactions.
29 . 10 . 23. Crusts scraped off and emulsified with a little saline in a mortar, and two fresh rabbits inoculated by scarification on each flank.
31 . 10 . 23. Distinct swelling and redness in rabbit of passage inoculation from Case V; much less reaction in rabbit of Case VI.
3 . 11 . 23. Crusts scraped off and emulsified in saline, and two young rabbits inoculated on flanks by scarification.
9 . 11 . 23. In about six days typical Jennerian papules appeared, and the rabbits proved immune to subsequent inoculation with vaccinia virus.

Expt. 2 (139, 1923). Rabbits; intratesticular method.

14 . 12 . 23. Inoculation into the right testicles of two rabbits of 1 c.c. of saline emulsions of brain from Case V and Case VI respectively.
15 . 12 . 23. Considerable swelling of testicles.
17 . 12 . 23. Swelling much less. Animals killed; testicles showed several small hæmorrhages, very suggestive of a vaccinial lesion. Emulsions were prepared from the testicles and a young male rabbit had 1 c.c. of the respective emulsions injected into the right and left testicles.
19 . 12 . 23. Well-marked swelling of both testicles.
20 . 12 . 23. Swelling greatly decreased.
In two or three days both testicles normal.

Expt. 3 (140, 1923). Rabbits; intratesticular method.

19 . 12 . 23. In repetition of the above experiment one rabbit received 1·5 c.c. of brain emulsion from Case V into the right testicle, the other 1·5 c.c. of brain emulsion from Case VI into the left.
20 . 12 . 23. Both testicles swollen half as large again.
21 . 12 . 23. Swelling greater. Animals killed. Testicles greatly enlarged, injected, œdematous and showing much hæmorrhage into their parenchyma, their appearance being typical of the lesion produced by testicular inoculation with vaccinia.
An emulsion was then prepared from the testicle that had been injected with brain from Case V, and four rabbits were inoculated as follows:

21 . 12 . 23. Inoculation into brain of two rabbits, on skin of a third and into testicle of a fourth.

The two rabbits inoculated intracerebrally showed a distinct rise of temperature after the inoculation, and were killed on the third and fourth days: both showed a mild meningo-encephalitis.

The testicular inoculation produced considerable swelling of the gland and hæmorrhages into its substance.

The skin of the scarified rabbit showed on 24 . 12 . 23 some redness, scales and two or three raised papules.

24 . 12 . 23. Inoculation into skin of another rabbit (Expt. 141A) of crusts collected from above.

27 . 12 . 23. Small papules had appeared; these were removed and inoculated into the skin of a small rabbit (Expt. 142, 1923).

Definite vaccinia papules were produced.

D. Investigation of Neurotrophic Properties of the Vaccinia Virus raised from Cases V and VI.

Expt. 1 (105, 1923). Four rabbits, A, B, C, D.

25 . 10 . 23. Inoculation intracerebrally of rabbits A and B with virus derived from the brain of Case V, and rabbits C and D with virus from the vaccination scab of Case VI. The viruses used in this experiment had been raised and kindly provided by Dr. Blaxall.

Rabbit A alone, inoculated with virus from brain of Case V, developed pyrexia (T. 103·8°) and died on the third day. The brain was removed, pieces were subjected to histological examination and the rest were preserved in 33 per cent. glycerine.

Expt. 2 (106, 1923). Two rabbits, A and B.

29 . 10 . 23. Intracerebral inoculation of rabbits A and B with an emulsion of brain of rabbit A (Expt. 105, 1923).

30 . 10 . 23. T.: A 103·4°. B 105·4°.

31 . 10 . 23. T.: A 103·8°. B found dead.

1 . 11 . 23. T.: A 103·4°.

2 . 11 . 23. T.: A 104·2°.

3 . 11 . 23. T.: A 104·2°; killed.

The brain of A was removed and found to be soft and slightly congested but otherwise apparently normal. Pieces were subjected to histological examination and the rest preserved in 33 per cent. glycerine.

Expt. 3 (114, 1923). Two rabbits, A and B.

7 . 11 . 23. Intracerebral inoculation of rabbits A and B with brain emulsion from rabbit A (Expt. 106, 1923).

8 . 11 . 23. T.: A 101·4°. B died.

9 . 11 . 23. T.: A 102·8°.

10 . 11 . 23. T.: A 104·6°.

12 . 11 . 23. T.: A 103·8°.

13 . 11 . 23. T.: A 103·6°; killed.

Brain of A removed for examination and an emulsion prepared.

Expt. 4 (118, 1923). Two rabbits.

13 . 11 . 23. Intracerebral inoculation of two rabbits with emulsion of brain from rabbit A (Expt. 3).

Both rabbits developed temperatures of 103° to 105° some days later.

Histological Examinations, Investigation D.—Microscopic examinations of the brains from Rabbit A, Expt. 1, Rabbit A, Expt. 2, and Rabbit A, Expt. 3, showed varying degrees of a meningo-encephalitis of the less intense type caused by the vaccinial virus as described on p. 205, but on the whole of slight degree.

Results of Investigation D.—In the above experiments a mild meningo-encephalitis was produced in rabbits by intra-cerebral inoculation of the vaccinia virus derived from the brain of Case V, and this encephalitis could be passed in series from one animal to another. The mildness of the encephalitis was shown by the type of lesion, by its tendency to remain localized, and by the general tendency for the animals to survive; further, unless the animals were killed within four or five days of the inoculation when the temperature was up, there was little chance of propagating the virus in series.

It cannot be adduced, however, from these experiments that the virus had any great neurotrophic affinities, as similar experiments with the ordinary calf-lymph can produce a very similar encephalitis.

Results of Dr. McIntosh's Experiments.

The experiments detailed above were undertaken with the object of determining the nature of the causative agent or agents. Ordinary cultural examinations gave mainly negative results, but in a few instances one or two colonies of a non-pathogenic bacterium appeared. This demonstrated that we had not to deal with any simple septic infection.

On account of the histological picture it was considered that *intracerebral inoculations* should be used for the main series of experiments (A). The inoculum consisted of emulsions of brain or cord in normal saline, and the animals employed were monkeys and rabbits. By the employment of both monkeys and rabbits it was hoped that the experiments would determine whether the virus of either poliomyelitis or encephalitis lethargica was present. Poliomyelitis in our experience is readily transmitted to monkeys and only with difficulty to rabbits, whilst the converse is true of encephalitis lethargica (McIntosh and Turnbull, 1913, 1920; McIntosh, 1918, 1920); recently some criticisms have been raised against this view of the infectivity of encephalitis lethargica, to which a reply has been made (McIntosh, 1924).

The intracerebral inoculation of material from Case III caused paresis of the right wrist in one macaque (Expt. 1*a*), a transient paresis in the other (Expt. 1*b*), and a rise of temperature in a rabbit (1*c*). A necropsy on the macaque (1*a*) showed a slight non-purulent meningo-encephalitis confined to the immediate neighbourhood of the needle track. The first passage experiments resulted in a transient weakness of the fore limbs in a macaque, and a rise of temperature and general illness in two rabbits. In one of these rabbits (*B*, Expt. 2) a meningo-encephalitis was found on microscopic examination. A second passage resulted in a slight rise of temperature in a rabbit (*B*, Expt. 5), whilst in a parallel experiment (4) intratesticular inoculations caused swelling of the testicles. These passage experiments are illustrated on the Chart. With the material from the convalescent Case IV the results were completely negative. The inoculations of material from Case V caused a transient weakness of the hind limbs in a macaque but no change in three rabbits. Material from Case VI caused no change in a macaque but a rise of temperature in one rabbit (*A*, Expt. 1*b*); in this rabbit a meningo-encephalitis was found on microscopic examination. A passage experiment proved negative.

In two rabbits, therefore, meningo-encephalitis was demonstrated histologically, following an initial inoculation in one and a first passage inoculation in the other. The inflammation involved the meninges more than the parenchyma, and was distinctly non-purulent in type. It resembled a mild reaction of the kind that follows injection of vaccinial virus, as described on p. 205. The characteristic changes that one of us (J. McI.) had observed in former successful inoculations of rabbits with the virus of poliomyelitis or of encephalitis lethargica were entirely absent.

A second series of experiments, C, was designed *to recover vaccinia virus* from the encephalitic brains; Ohtawara (1922) and others have shown that vaccinia virus is distributed throughout the tissues, and may persist therein for a considerable time after vaccination. Material from Cases V and VI was employed. The results obtained by dermal and intratesticular inoculation showed definitely that the virus of vaccinia was present in the brains of these cases. Inoculation into the brains of rabbits of the vaccinia virus recovered from these cases produced a mild encephalo-myelitis, and this (Investigation D) was carried on in series in rabbits for one to two passages. This encephalitis was very similar in character to that produced by direct injections of emulsions of the encephalitic brains, but was more severe. It was, however, mild.

In a third series of experiments, D, the *neurotropic properties of the vaccinia virus* recovered from Case V were examined. The results did not demonstrate any great neurotropic affinity.

The three series of experiments show that it is most improbable that the encephalitis was due to the virus of poliomyelitis or of encephalitis lethargica, and that the only virus demonstrable was that of vaccinia.

CONCLUSIONS.

In the preceding pages have been given the clinical histories and post-mortem findings in seven examples of an encephalo-myelitis following vaccination, and the clinical histories in three other examples.

In view of the close resemblance between the clinical manifestations, the uniformity of the histological changes and the absence of similar cases independent of vaccination there can be no doubt that vaccination was a definite causal factor.

The source of the lymph differed in different cases, so that it is unlikely that the lymph was contaminated. There was no histological evidence of contamination of the vaccination wounds, the inflammatory reaction in the scabs and regional glands appearing to be that of vaccinia of somewhat exceptional intensity; that the encephalitis was due to pyogenic contamination is excluded by the histological examinations and bacterial cultures. Evidence of extension of the infection along the nerves from the vaccinated areas to the spinal cord was not found histologically.

Histologically the encephalo-myelitis belongs to the non-purulent group, and among the known members of that group finds its closest affinity in poliomyelitis and encephalitis lethargica. The available data do not show a relationship between the incidence of the post-vaccinial encephalitis and encephalitis lethargica such as has recently been described in Holland (Bastiaanse, etc., 1925). The illness and its sequelæ differ conspicuously from those of poliomyelitis; the differences are less marked in the case of lethargic encephalitis, but appear to be definite. The post-vaccinial encephalo-myelitis differs histologically from that of poliomyelitis in distribution, sites of maximal incidence and especially in detail. A conspicuous peculiarity is the presence of broad zones of softening round vessels in the white matter. If post-vaccinial encephalo-myelitis is due to a modification of poliomyelitis by vaccinia, profound changes have been caused in the histology. The encephalo-myelitis differs histologically from that of encephalitis lethargica still more in distribution and sites of maximal incidence, but less in detail; here again the zones of perivascular softening are a conspicuous peculiarity. If the virus of encephalitis lethargica plays a part in post-vaccinial encephalo-myelitis, it has caused definite modifications of the histological picture.

The experimental investigation showed that the virus of vaccinia was not only present in the scabs and axillary glands, but could be recovered from the brains. From the results of intra-cerebral inoculation of monkeys and rabbits it is most improbable that the encephalitis was due to the virus of polio-myelitis or of encephalitis lethargica. The inoculation seldom gave rise to an encephalitis; when it did, the inflammation appeared to be a mild example of that caused by the virus of vaccinia, for instance the vaccinial virus recovered from the patients' brains. But experiment did not demonstrate that the virus recovered from the brains had specially great neurotropic properties.

The virus of vaccinia was, therefore, alone demonstrated by the experiments. The inflammatory reaction in the immediate neighbourhood of the sites of vaccination appeared to be unusually intense, but no general vaccinia of the skin and no visceral lesions specific of vaccinia or variola were found in the patients. Although vaccinial encephalitis can be caused experimentally in rabbits, such an encephalitis has not been recognized in man. But the virus of vaccinia is very closely allied to, if not identical with, the virus of variola; and the examination of the literature shows that variola has frequently, though relatively seldom, been complicated by inflammations of the brain and spinal cord that were clinically unlike pyogenic infections or have been proved microscopically to be non-pyogenic. Such complications have occurred in both mild and severe variola, and at all stages of the disease. In most of the recorded examples the patients survived, and the symptoms cleared up or permanent disturbances were left that usually gave a clinical picture not yet recorded after post-vaccinial encephalo-myelitis. But necropsies were obtained in a small group of six cases in which a paraplegia was combined with paralysis of the bladder and rectum. The spinal cord was examined microscopically: no histological abnormality was found in two, but in four a myelitis is described which is very similar to that in the post-vaccinial cases.

SUMMARY.

The seven cases of encephalo-myelitis were definitely connected with vaccination. The histological changes in the central nervous system were allied to those of poliomyelitis and encephalitis lethargica, but showed characteristic differences. The clinical picture was also peculiar. The only virus demonstrated experimentally in the tissue of brain and cord was a vaccinial virus. Experiment did not prove this virus to have neurotropic properties of exceptional intensity. Vaccinial encephalitis can be caused experimentally in animals; the possibility of a similar encephalitis in man is suggested by the literature of infection with the closely allied or identical virus of variola, cases having been recorded in which variola and varioloid were complicated by an

apparently specific encephalo-myelitis. This encephalo-myelitis of variola appears to have been very similar histologically to that in the seven cases under investigation.

We are indebted to the Medical Research Council for defraying part of the expenses of illustration.

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DESCRIPTION OF PLATES.

Fig. 1.—Adventitial and perivascular infiltration of cerebral cortex. Left Rolandic region, Case II. Hæmatoxylin and eosin. Obj. 1″; oc. Zeiss 4.

Fig. 2.—Perivascular infiltration, without softening, of cerebral medulla. Left prefrontal region, Case III. Hæmatoxylin and eosin. Obj. $\frac{1}{6}$″; oc. Zeiss 4.

Fig. 3.—Infiltration of pontine nuclei. Pons at level of trigeminal roots, Case II. Hæmatoxylin and eosin. Obj. 1″; oc. Zeiss K 6.

Fig. 4.—Perivascular softening in white matter of spinal cord. Second thoracic segment, Case III. Weigert's iron-hæmatoxylin and van Gieson.

Fig. 5.—Infiltration of lumbar cord, Case V. Hæmatoxylin and eosin; lightly stained so that the perivascular softening in the white matter is not demonstrated.

Fig. 6.—Perivascular softening in white and infiltration of grey matter. Lateral aspect of ventral horn with white matter of fourth lumbar segment of spinal cord, Case III. Weigert's iron-hæmatoxylin and van Gieson. Obj. $\frac{2}{3}$″; oc. Zeiss 4.

Fig. 7.—Perivascular softening in white matter. Posterior white column, thoracic cord, Case I. Weigert's iron-hæmatoxylin and van Gieson. Obj. $\frac{1}{6}$″; oc. Zeiss K 6.

Fig. 8.—Commencement of healing of perivascular softening in white matter. Ventro-mesial white column, fourth cervical segment of spinal cord, Case IV. Weigert's iron-hæmatoxylin and van Gieson. Obj. $\frac{1}{6}$″; oc. Ziess 4. Note the foam-cells in adventitia and the early gliosis.

Fig. 9.—To illustrate cells described in adventitial infiltrations. Ventral commissure, cervical cord, Case V. Hæmatoxylin and eosin. Obj. $\frac{1}{12}$″; oc. Zeiss 4. *sl.* = small lymphocytes. *ll.* = large lymphocytes. *pd.* = plasmacytoid cell. *f.* = cell with nucleus of fibrocytic type. *h.* = hyaline cells (note overlapping lobes in nuclei). *hm.* = hyaline cell in blood (large mononuclear or endothelial leucocyte). *p.* = polymorphonuclear neutrophil leucocytes.

Fig. 10.—Emigration of neutrophil leucocytes. Ventral horn, fourth lumbar segment, Case III. Jenner's stain. Obj. $\frac{1}{12}$″; oc. Zeiss K 6. The pink "neutrophil" granules are indicated in black.

Fig. 1.

Turnbull and McIntosh.

FIG. 2.

Turnbull and McIntosh.

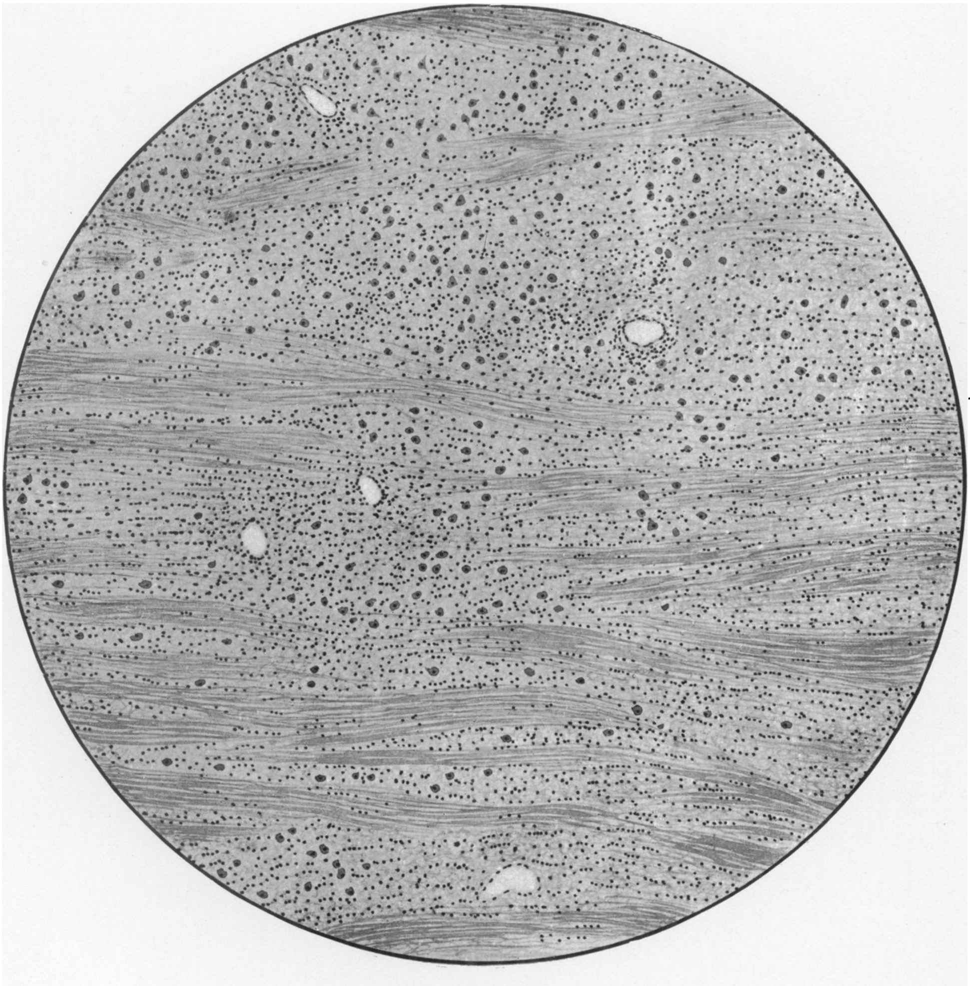

Fig. 3.

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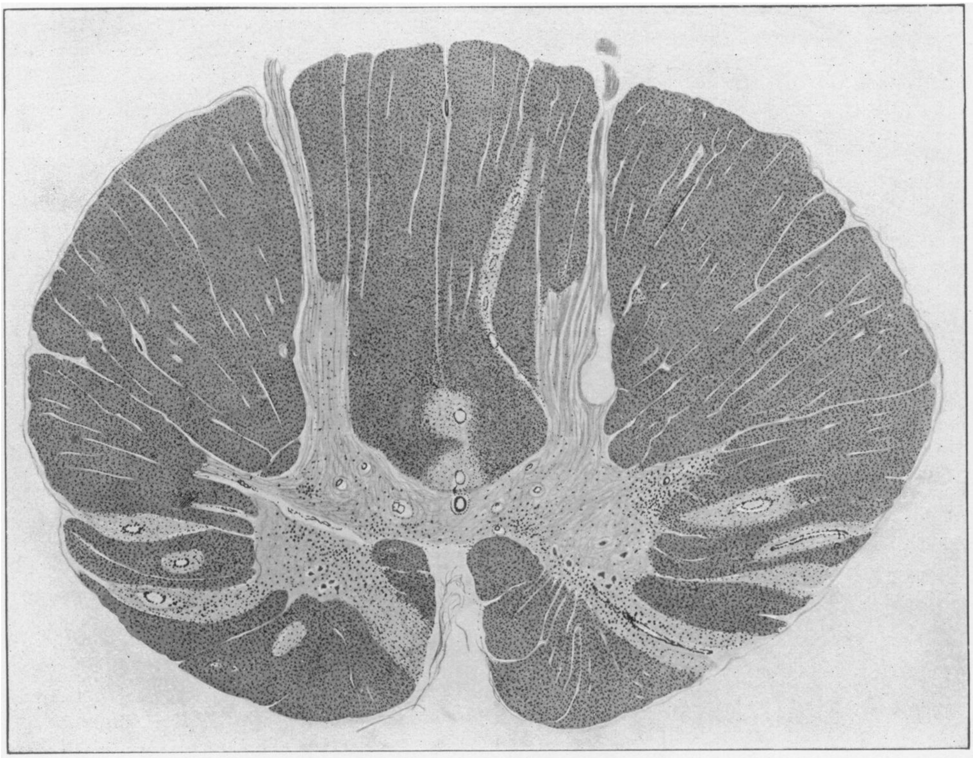

Fig. 4.

Turnbull and McIntosh.

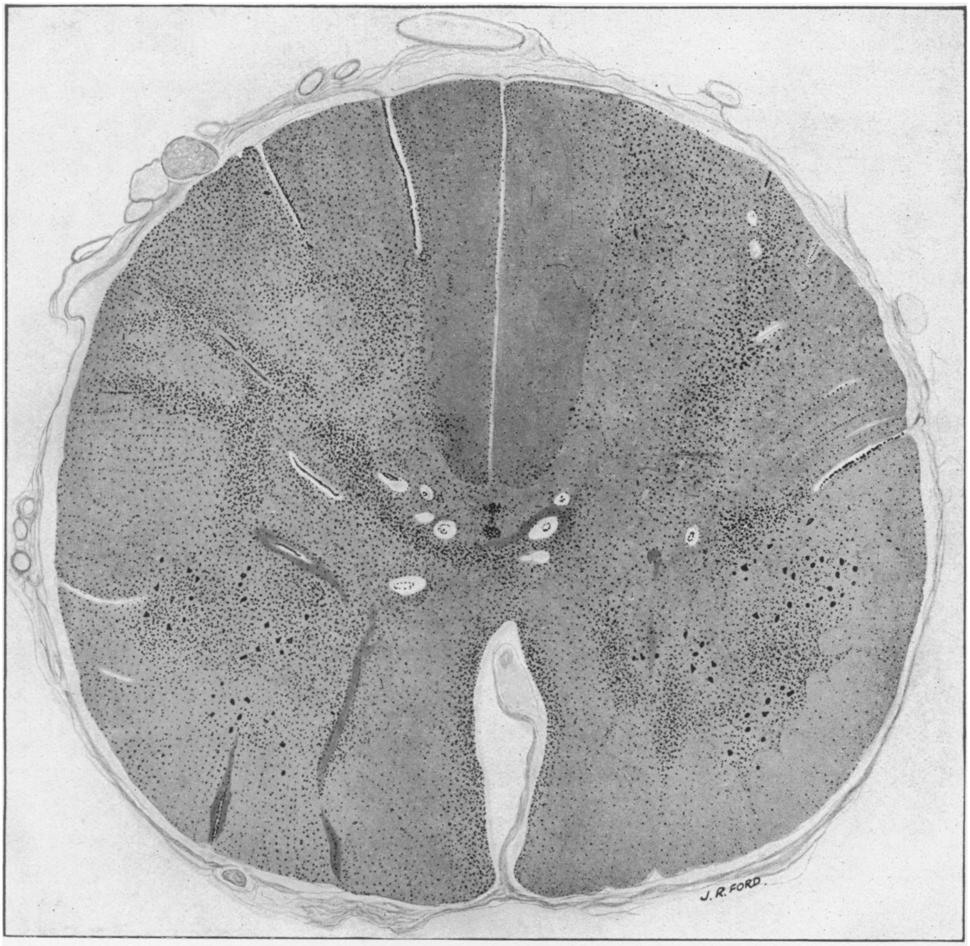

Fig. 5.

Turnbull and McIntosh.

Fig. 6.

Turnbull and McIntosh.

FIG. 7.

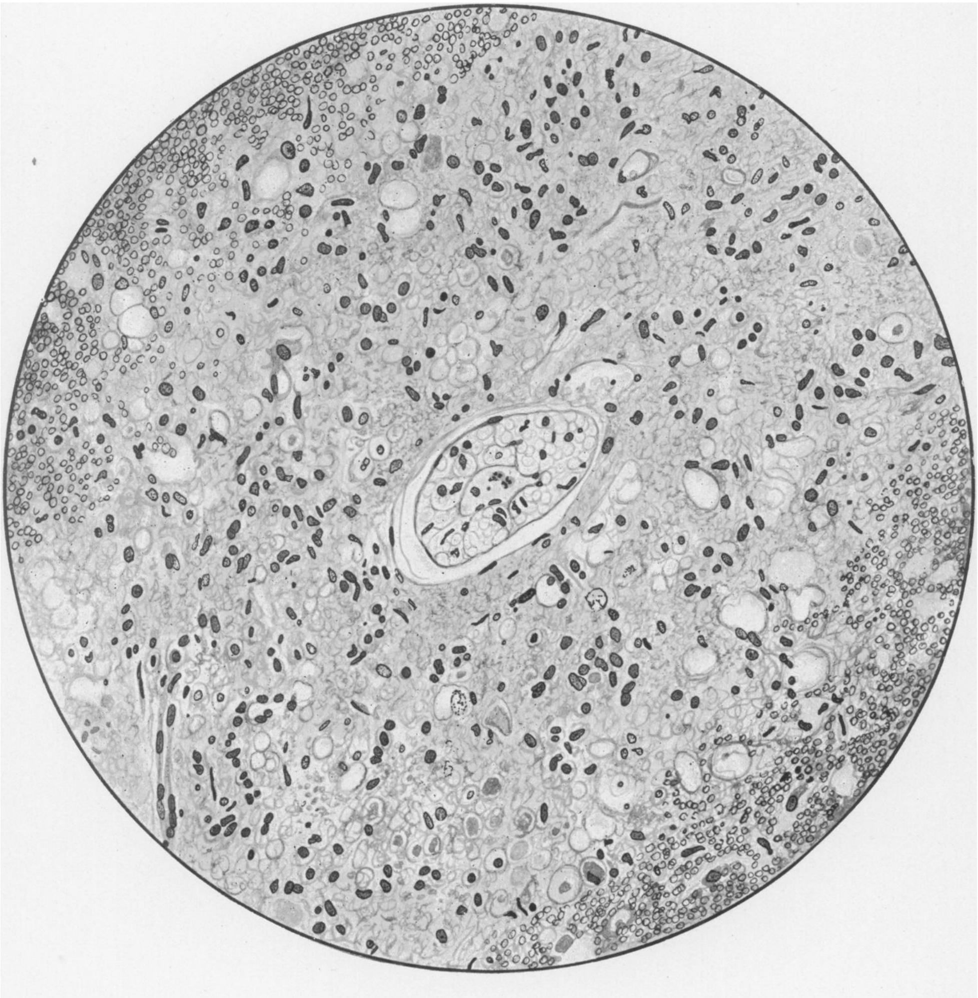

FIG. 8.

Turnbull and McIntosh.

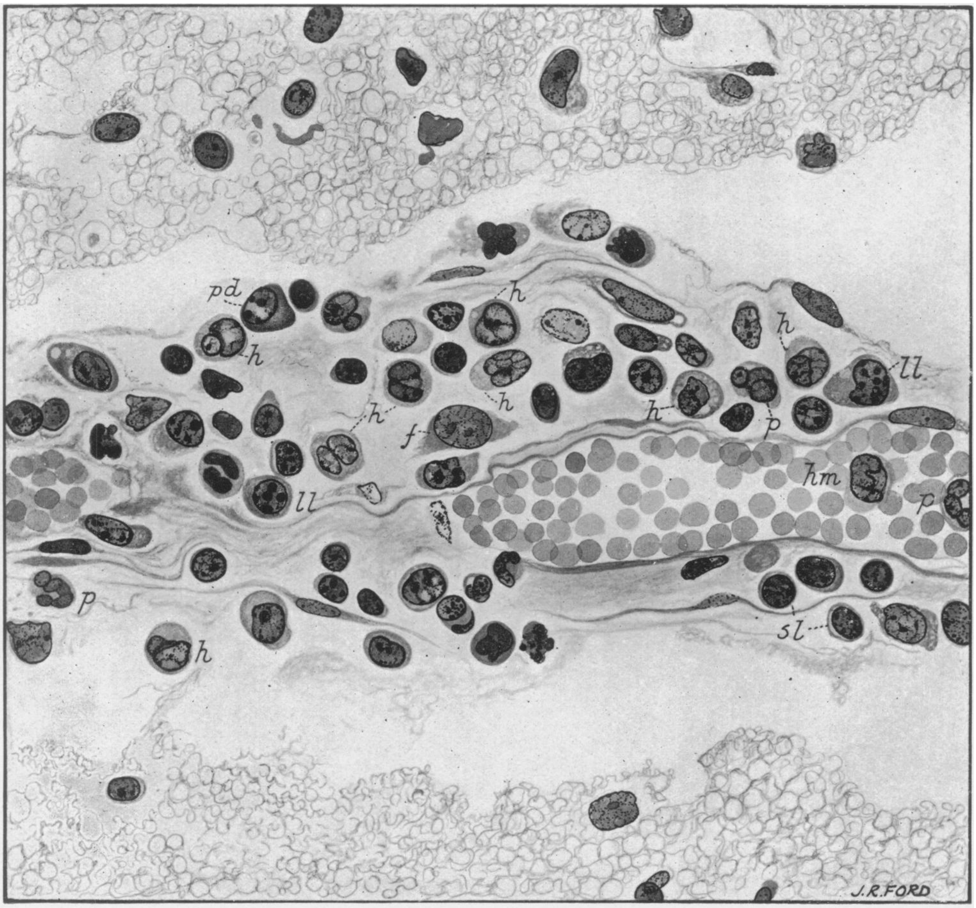

Fig. 9.

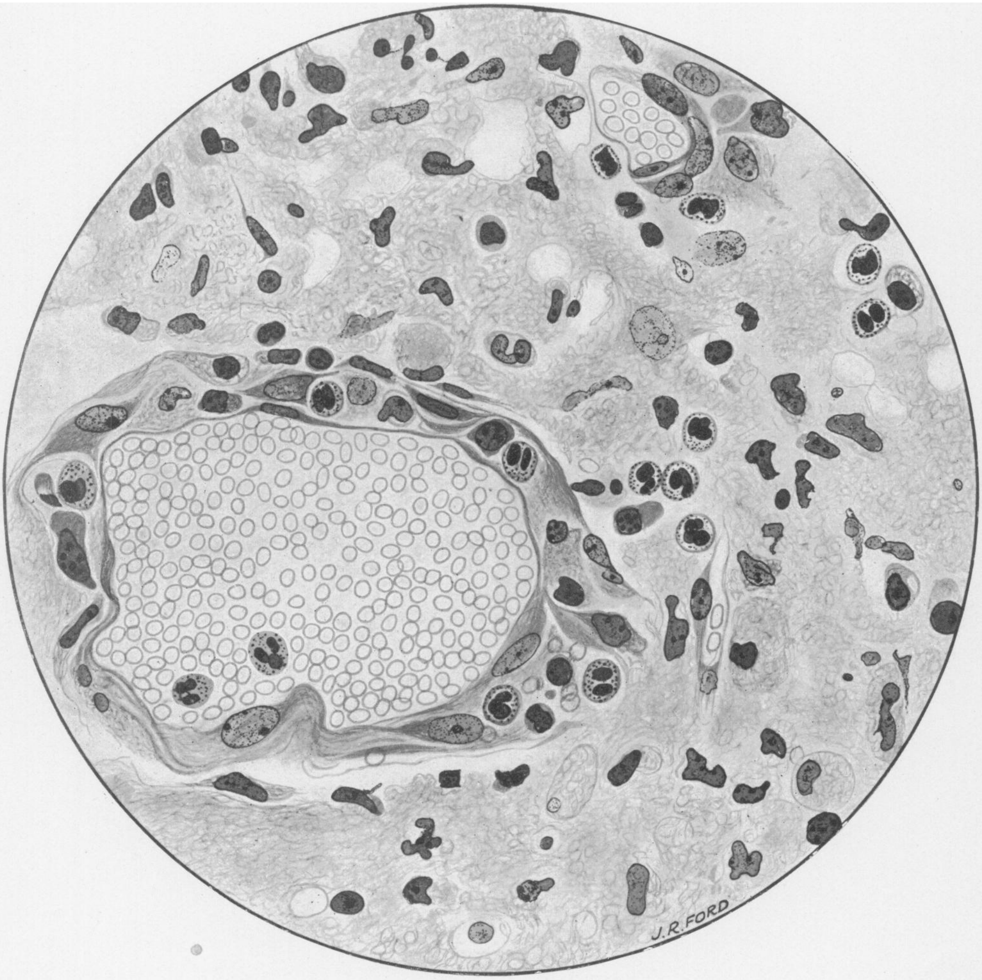

FIG. 10.

Turnbull and McIntosh.